Ruthenium- and Cobalt-Catalyzed Chelation-Assisted C–H Functionalizations

Dissertation

for the award of the degree

“Doctor rerum naturalium”

of the Georg-August-Universität Göttingen

within the doctoral program of chemistry

of the Georg-August University School of Science (GAUSS)

Submitted by

Ruhuai Mei

From Huanggang (China)

Göttingen, 2017

Thesis Committee

Prof. Dr. Lutz Ackermann, Institute of Organic and Biomolecular Chemistry

Prof. Dr. Franc Meyer, Institute of Inorganic Chemistry

Members of the Examination Board

Reviewer: Prof. Dr. Lutz Ackermann, Institute of Organic and Biomolecular Chemistry

Second Reviewer: Prof. Dr. Franc Meyer, Institute of Inorganic Chemistry

Further Members of the Examination Board

Prof. Dr. Manuel Alcarazo, Institute of Organic and Bimolecular Chemistry

Prof. Dr. Inke Siewert, Institute of Inorganic Chemistry

Dr. Franziska Thomas, Institute of Organic and Bimolecular Chemistry

Prof. Dr. Ulf Diederichsen, Institute of Organic and Bimolecular Chemistry

Date of the oral examination: August 31st, 2017

Contents

Abbreviations

Ac	acetyl	Et	ethyl
Ad	adamantyl	EWG	electron-withdrawing group
Alk	alkyl	FG	functional group
AMLA	ambiphilic metal-ligand activation	FTICR	Fourier transform ion cyclotron resonance
Ar	aryl	GC-MS	gas chromatography-mass spectrometry
ATR	attenuated total reflectance	Hept	heptyl
Bn	benzyl	HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
Bu	butyl	HMPT	tris(dimethylamino)phosphine
cat	catalytic	HRMS	high resolution mass spectrometry
CMD	concerted metalation-deprotonation	HASPO	heteroatom-substituted secondary phosphine oxides
cod	1,5-cyclooctadiene	IES	internal electrophilic substitution
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl	IR	infrared
CV	cyclic voltammetry	*J*	coupling constant
Cy	cyclohexyl	KIE	kinetic isotope effect
DCE	1,2-dichloroethane	L	ligand
DG	directing group	M	metal
DMA	*N*,*N*-dimethylformamide	Mes	2,4,6-trimethylphenyl
DMAP	4-(dimethylamino)pyridin	Me	methyl
DMSO	dimethylsulfoxide	*m*	*meta*
DPPH	2,2-diphenyl-1-picrylhydrazyl	M.p.	melting point
EDG	electron-donating group	MPAA	mono-*N*-protected amino acid
EI	electron ionization	NBS	*N*-bromosuccinimide
equiv	equivalents	NCS	*N*-chlorosuccinimide
ESI	electronspray ionization	NIS	*N*-iodosuccinimide

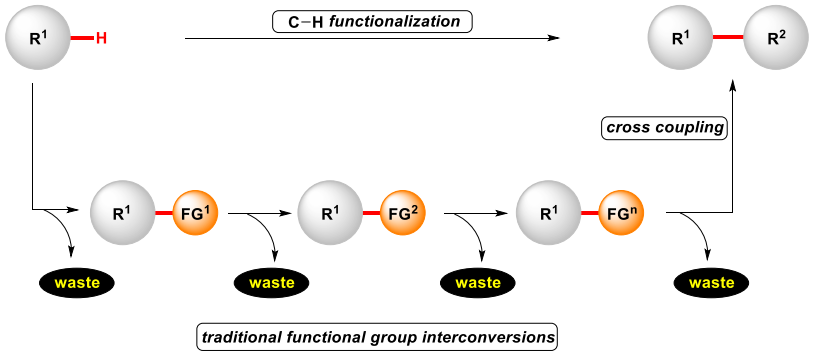
Abbreviations

NMP	*N*-methyl-2-pyrrolidinone	SPO	secondary phosphine oxide
NMR	nuclear magnetic resonance	T	temperature
o	*ortho*	*t*-Am	2-methylbut-2-yl
p	*para*	TBDMS	*tert*-butyldimethylsilyl
PA	phosphinous acid	TBS	tri-*n*-butylsilyl
PEG	polyethylene glycol	TEMPO	2,2,6,6-tetramethylpiperidinyloxyl
Ph	phenyl	Tf	trifluoromethanesulfonyl
Piv	2,2-dimethylpropanoyl	TFE	2,2,2,-trifluoroethanol
pKa	logarithmic acid dissociation constant	THF	tetrahydrofuran
PMP	*para*-methoxyphenyl	TIPS	triisopropylsilyl
Pr	propyl	TM	transition metal
py	pyridine	TMP	2,4,6-trimethoxyphenyl
PyO	2-aminopyridine-1-oxide	TMS	trimethylsilyl
Q	8-aminoquinolin	TOF	time of flight
δ	chemical shift	TON	turnover number
S_EAr	electrophilic aromatic substitution	TS	transition state
SET	single electron transfer	Ts	tosyl
S_N1	first-order nucleophilic substitution	UV	ultraviolet
S_N2	second-order nucleophilic substitution	XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

1 Introduction

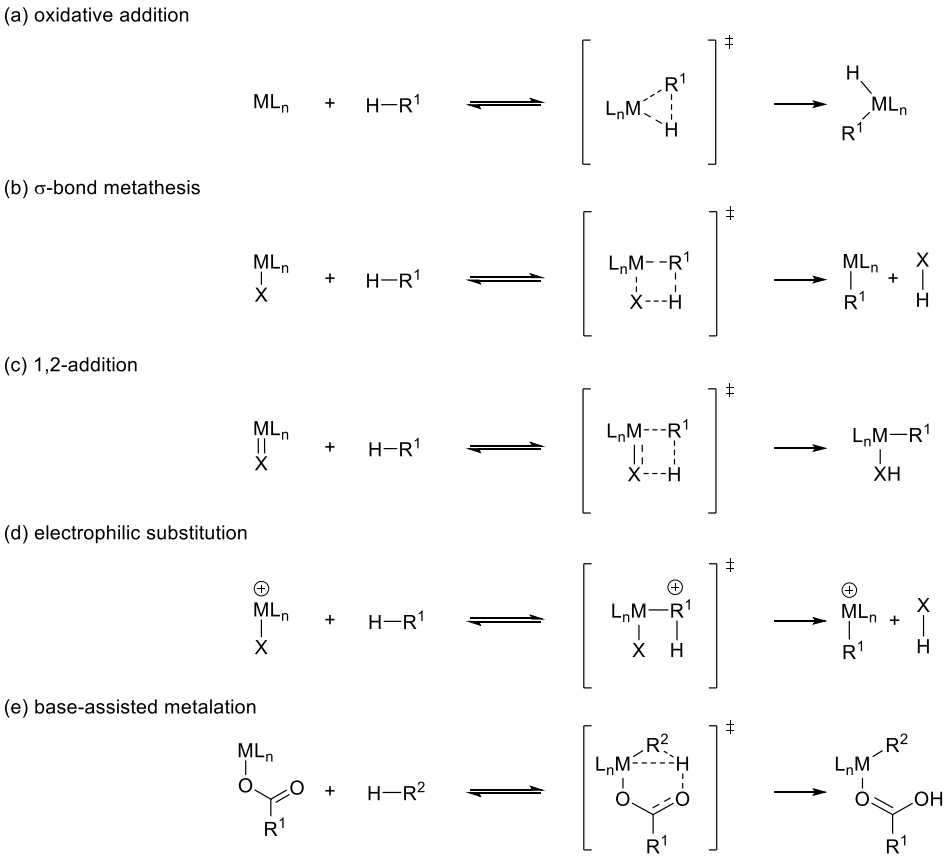
1.1 Transition Metal-Catalyzed C–H Functionalizations

Transition metal-catalyzed cross-coupling reactions of organic electrophiles and organometallic reagents have emerged as a tremendously powerful synthetic tool, and the development has reached a level of sophistication that allows for a wide range of coupling partners to be combined efficiently.[1] The importance of this general class of reactions was recognized by awarding of the Nobel Prize in chemistry to Richard Heck, Ei-ichi Negishi, and Akira Suzuki "for palladium-catalyzed cross-couplings in organic synthesis". Despite the enormous advances achieved by cross-coupling reactions, limitations still need to be addressed. For traditional cross-coupling reactions, a prefunctionalisation of substrates is necessary. These pre-functionalisation steps, along with the cross-coupling itself, are each accompanied by the generation of stoichiometric amounts of byproducts. In recent decades, the direct functionalization of otherwise inert C–H bonds was recognized as a potential alternative for traditional cross-coupling reactions due to its step- and atom- economy (Scheme 1).[2]



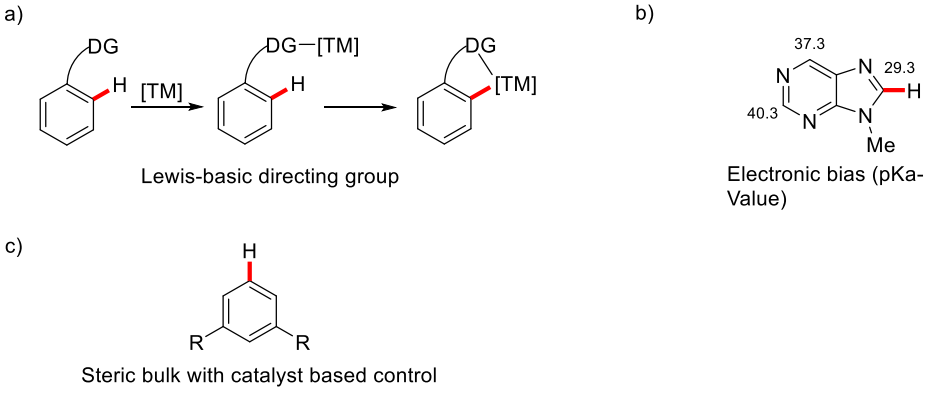
Scheme 1. C–H Functionalization *versus* functional group interconversions.

For the key C–H metalation step, several different mechanistic pathways have so far been widely accepted.[3] They are: a) oxidative addition with electron-rich, low-valent late-transition metal catalysts, such as iridium, platinum and ruthenium; b) σ-bond metathesis with early transition metals and lanthanoids; c) 1,2-addition to unsaturated M=X bonds, where a heteroatom is a hydrogen acceptor, for some early or mid-transition metals; d) electrophilic substitution with late-transition metals in higher oxidation states; e) base-assisted deprotonation, for example, using secondary phosphine oxides or carboxylates as an internal base (Scheme 2). Based on a six-membered transition state, the last pathway has been called either concerted metalation-deprotonation (CMD)[4] or ambiphilic metal ligand activation (AMLA).[3c, 5] Whereas a four membered transition state is proposed in case of an internal electrophilic substitution (IES), which was found to be most likely for C–H activations enabled by complexes with alkoxy ligands.[6] A novel base-assisted internal electrophilic substitution (BIES) has recently been proposed for electron-rich arenes with acetate or carboxylate ligands.[7]



Scheme 2. Plausible mechanistic pathways for C–H activation.

An important issue in C−H activation chemistry is the chemo- and site-selectivity. The organic molecules of interest usually possess many C–H bonds with similar dissociation energies. Therefore, achieving chemo- and regio-selective functionalization is challenging. In order to differentiate between various chemically similar C–H bonds, several strategies have been developed. These include a) differentiation through assistance of a Lewis-basic directing group (DG) within the substrate, b) differently electronically activated C–H bonds,[8] and c) sterical-bulk in combination with catalyst control (Scheme 3).[9]



Scheme 3. Strategies for site-selectivity in C–H functionalization.

1.2 Ruthenium-Catalyzed C–H Arylation

Substituted (hetero)biaryls are central structural motifs in various compounds with activities of relevance to different areas, such as pharmaceutical or material sciences.[10] A variety of industrially important pharmaceuticals or agrochemicals have a biaryl as indispensable subunit (Figure 1).[11]

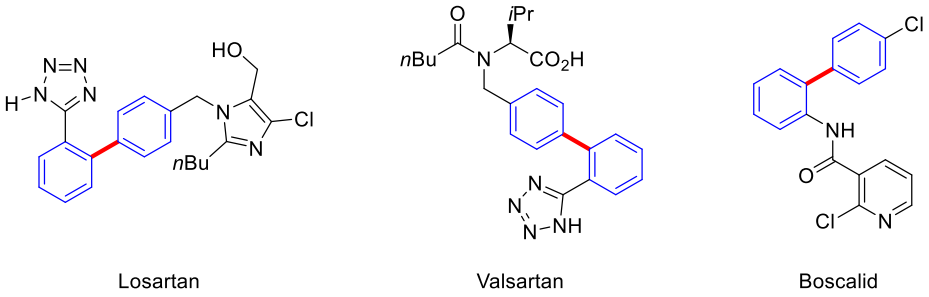
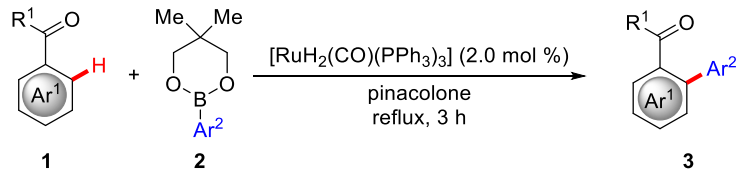


Figure 1. Representative examples for bioactive biaryls.

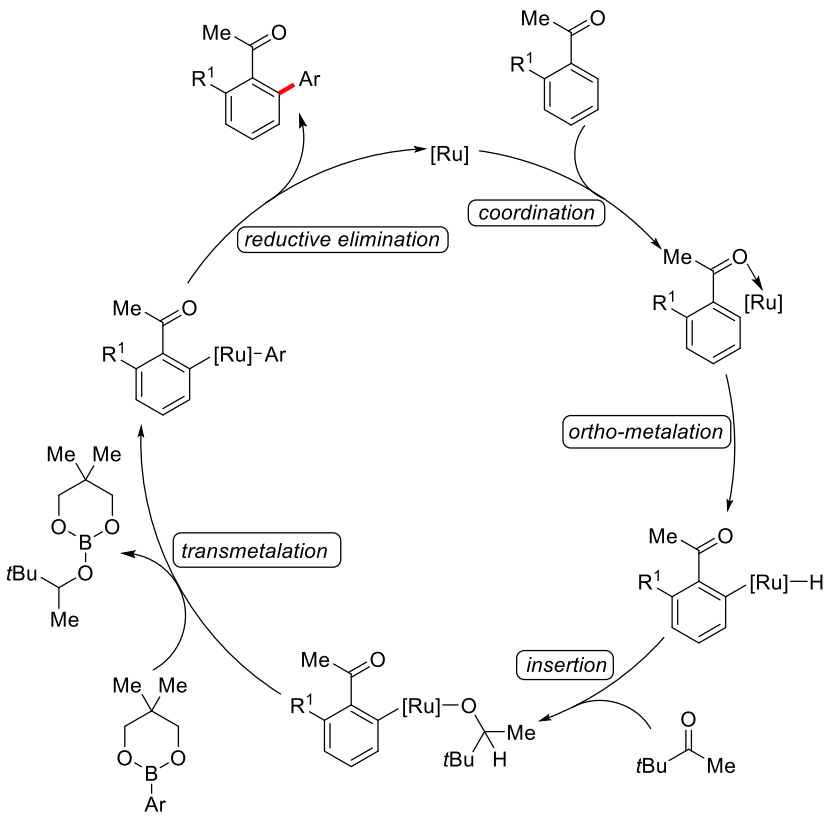
In the past decades, traditional cross-coupling reactions have emerged as reliable methodologies for the preparation of biaryl compounds.[12] However, these transformations usually require prefunctionalized substrates, which involve a number of synthetic operations. Therefore, direct arylation reactions through the cleavage of an otherwise inert C–H bond represent an economically and environmentally more attractive strategy.[13] Importantly, catalytic C–H arylation improves the step- and atom-economy of the cross-coupling process.

1.2.1 Ruthenium Catalyzed C–H Arylation with Aryl Boronates

In 2003, Kakiuchi and co-workers reported the ruthenium(0)-catalyzed direct arylation of ketones **1** with aryl boronates **2** as the coupling partners (Scheme 4).[14] Thus, a series of aryl ketones **1** were efficiently arylated in pinacolone as the solvent. The detailed mechanistic studies by Kakiuchi, Chatani *et al*. suggested that the solvent pinacolone served as a sacrificial oxidant (Scheme 5).[15] Subsequently, this protocol was also applied to the catalytic functionalization of challenging C(sp^3)–H bonds.[16] The efficiency of this strategy was further demonstrated by the regioselective 4-fold direct arylation of perylene bisimide (PBI) and anthraquinone.[17]

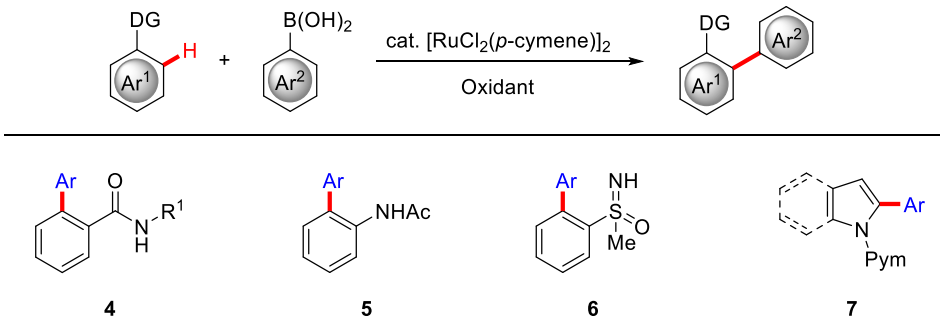


Scheme 4. Ruthenium-catalyzed direct arylation with boronate.



Scheme 5. Proposed mechanism for ruthenium-catalyzed direct arylation with boronates.

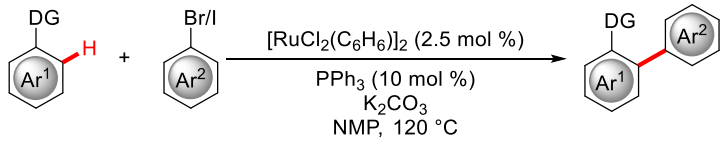
In addition to the above mentioned aryl boronates, more atom-economical aryl boronic acids could also be utilized as effective arylating reagents when the appropriate oxidants were employed under ruthenium(II)-catalyzed arylation reaction conditions (Scheme 6).[18]



Scheme 6. Ruthenium-catalyzed C–H arylation with aryl boronic acids as arylating reagents.

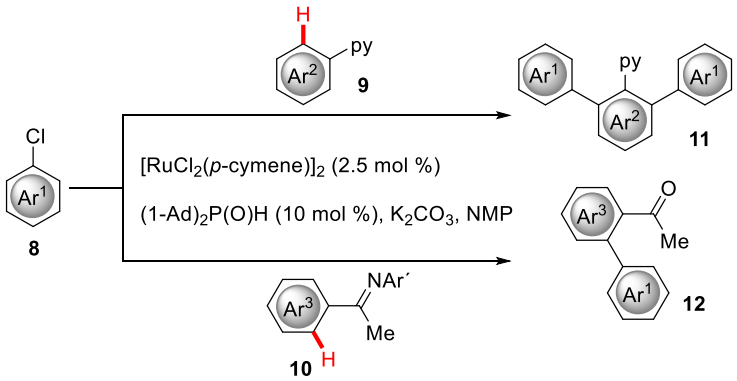
1.2.2 Ruthenium-Catalyzed C–H Arylation with Aryl (pseudo)Halides and Their Derivatives

In early reports, Oi and Inoue *et al*. developed a catalytic system consisting of $[RuCl_2(C_6H_6)]_2$ and PPh_3. The direct arylation of 2-phenylpyridine derivatives with aryl bromides or iodides was achieved with this protocol (Scheme 7).[19] In the next few years, this strategy was further applied to a series of other *N*-containing directing groups, such as imine, oxazoline, imidazoline, pyrazole and purine.[20] However, it was found that this catalytic system gave irreproducible results, which was later shown to be due to impurities in the solvent NMP.[21]



Scheme 7. Ruthenium-catalyzed arylation with phosphine ligand.

Compared to aryl bromides or iodides, aryl chlorides **8** are undoubtedly the most useful aryl halides as a single class of electrophilic substrates due to their lower cost and wider diversity.[22] However, aryl chlorides were generally unreactive under the catalytic system developed by Oi and Inoue. The lower reactivity of aryl chlorides is usually attributed to the higher bond strength of the C–Cl bond (bond dissociation energies for Ph–X: Cl: 96 kcal/mol; Br: 81 kcal/mol; I: 65 kcal/mol), which leads to a reluctance of aryl chlorides to oxidatively add to transition metal centers.[23]



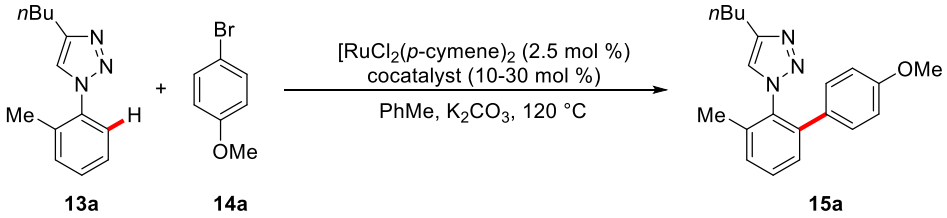
Scheme 8. Ruthenium-catalyzed direct arylation with aryl chlorides.

The first generally applicable method for intermolecular direct arylation with inexpensive aryl chlorides **8** was reported by Ackermann (Scheme 8).[24] In this case, the air-stable adamantyl-substituted secondary phosphine oxide (SPO) $(1\text{-Ad})_2P(O)H$ was used as the preligand, which enabled the unprecedented ruthenium-catalyzed diarylation of pyridines **9** and mono-arylation of imines **10** *via* C–H activation using diversely substituted aryl

chlorides **8**. With the assistance of HASPO ligands,[2q] moisture-stable and inexpensive aryl tosylates[25] or even phenols[26] proved to be viable (pro)electrophiles for similar transformations.

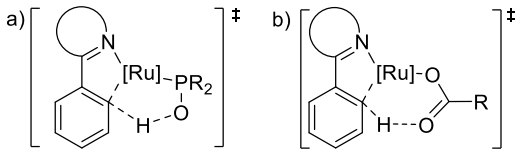
In 2008, Ackermann *et al.* first described the beneficial effect of a substoichiometric amount of carboxylic acid ligands in the ruthenium-catalyzed direct arylation of arenes, enabling reactions to occur even in the apolar solvent toluene (Table 1).[27] As shown in the Table 1, both (HA)SPO and carboxylate ligands showed high catalytic efficiency (entries 4 and 7). The authors proposed that the activation mechanisms were similar in both cases, proceeding *via* a base-assisted metalation process (Scheme 9). [27]

Table 1. Ruthenium-catalyzed direct arylation of triazole **13** in PhMe.



13a **14a** **15a**

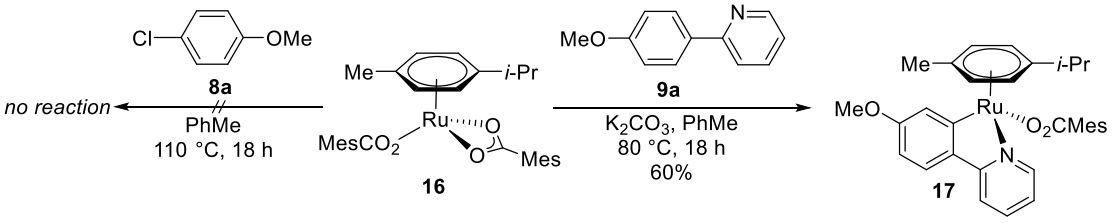
Entry	Cocatalyst	Isolated yield (%)
1	---	---
2	IPr·HCl	9
3	PPh_3	20
4	**$(1\text{-Ad})_2P(O)H$**	**85**
5	*t*-$BuCO_2H$	66
6	*i*-$PrCO_2H$	69
7	**$MesCO_2H$**	**93**



Scheme 9. Base-assisted ruthenation with a) Phosphinous acid and b) Carboxylate assistance.

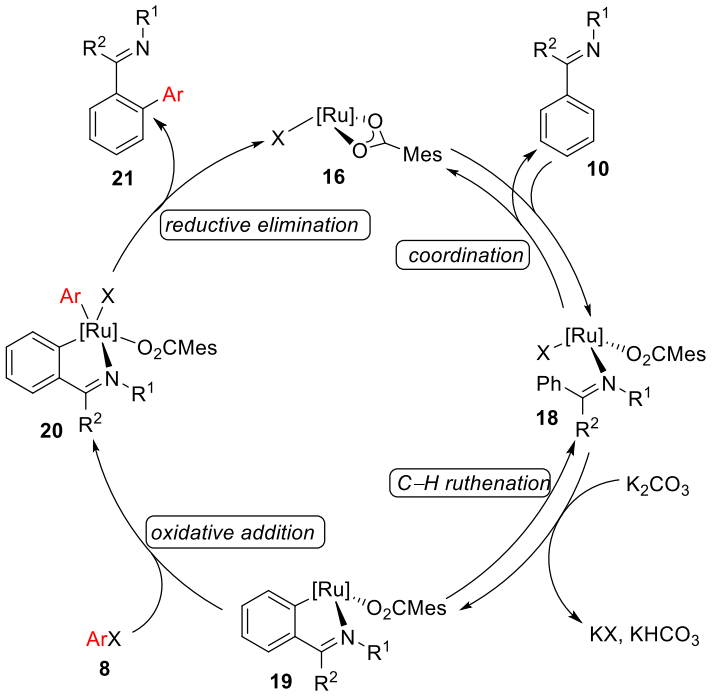
Stoichiometric experiments were carried out for mechanistic studies subsequently.[28] The well-defined ruthenium(II) biscarboxylate complex **16** was easily prepared by the treatment of $[RuCl_2(p\text{-cymene})]_2$ with $MesCO_2H$. The complex **16** proved to be catalytically competent even in the apolar solvent toluene, and displayed a remarkably broad substrates scope in the direct arylation of arenes. Importantly, no oxidative addition of *p*-chloroanisole **8a** to the ruthenium complex **16** was observed even at elevated temperature;

contrarily, cyclometalation of arene **9a** occurred easily, thereby yielding catalytically competent cyclometalated complex **17** (Scheme 10).



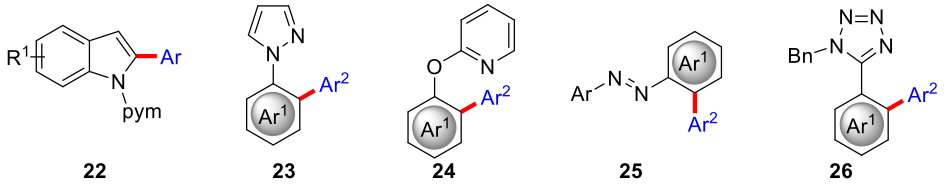
Scheme 10. Stoichiometric experiments with well-defined ruthenium complex **16**.

Based on these observations, a catalytic cycle was proposed as follow: First, complex **16** undergoes an initial reversible cyclometalation through a carboxylate-assisted deprotonation. Thereafter, complex **19** reacts in the rate-limiting step with aryl halide **8** to yield intermediate **20**. Finally, reductive elimination delivers the final products **21** and regenerates the active catalyst **16** (Scheme 11).[28]



Scheme 11. Proposed mechanism of carboxylate-assisted ruthenium-catalyzed direct arylations.

Subsequently, various important carboxylate-assisted ruthenium-catalyzed directed C–H arylation reactions were reported by Ackermann and coworkers (Scheme 12).[2f, 2l, 18b, 29]

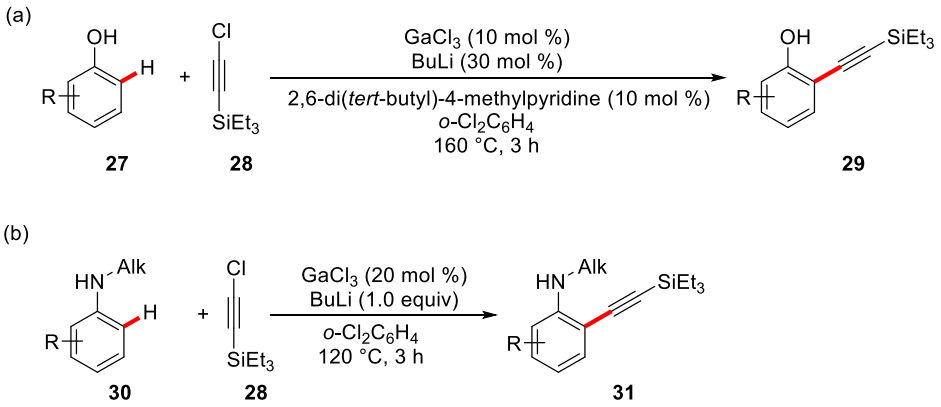


Scheme 12. Selected products of carboxylate assisted ruthenium-catalyzed directed C–H arylation.

1.3 Transition Metal-Catalyzed C–H Alkynylations

Alkynylarenes are versatile building blocks in organic synthesis.[30] As a consequence, the development of efficient strategies for the construction of alkynes continues to be an important goal.[31] The most frequently utilized method for the preparation of alkynylarenes is the Sonogashira-Hagihara reaction, in which C(aryl)–C(sp) bonds are constructed by the palladium/copper-catalyzed cross-coupling of aryl halides with terminal alkynes.[32] However, in recent years, transition metal-catalyzed C–H functionalization has emerged as a powerful alternative for the direct introduction of the alkynyl moiety.[33]

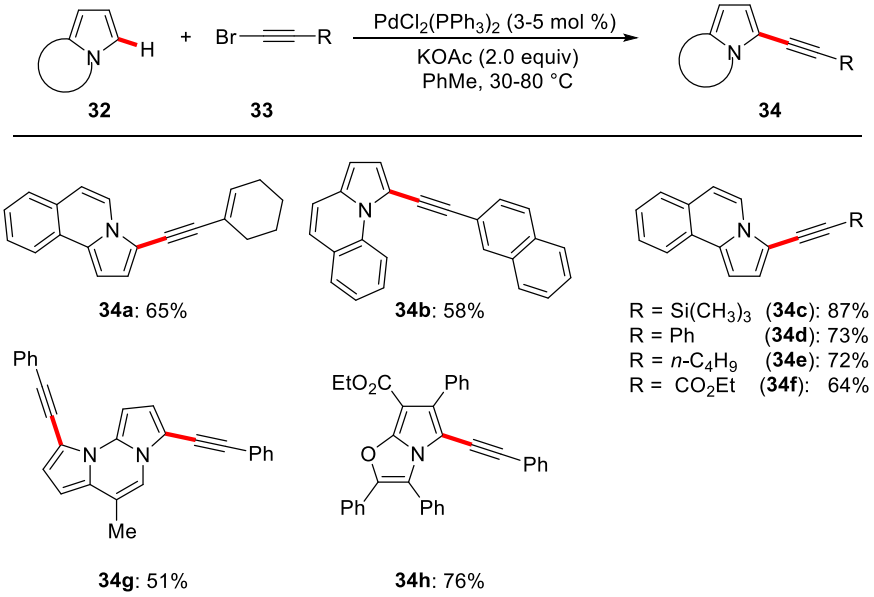
Early examples of direct C–H alkynylation reactions were reported by Yamaguchi *et al*. using $GaCl_3$ as catalyst (Scheme 13).[34] However, these transformations usually proceeded under harsh reaction conditions and highly reactive organolithium reagents are required. Thus, a variety of valuable functional groups were not compatible with this system.



Scheme 13. $GaCl_3$-catalyzed *ortho*-ethynylation reaction of phenols and *N*-alkylanilines.

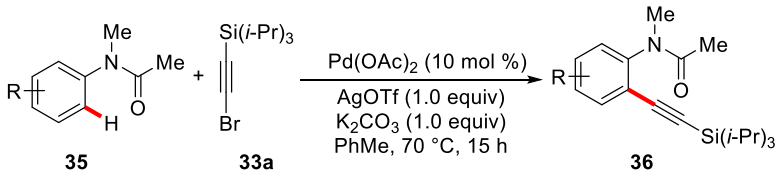
In 2007, Gevorgyan and cowokers reported a mild and effective method for palladium-catalyzed C–H alkynylation of electron-rich heterocycles (Scheme 14).[35] Thus, a series of heterocycles such as indolizine, pyrroloquinoline, pyrroloisoquinoline, pyrrolooxazole, and bis-pyrrolo-pyrimidine were successfully alkynylated. It was shown that a variety of functional groups at the bromoalkyne, such as alkyl, alkenyl, aryl, silyl, and ester, were perfectly tolerated. The authors proposed that this transformation operated *via* an electrophilic substitution pathway, analogous to that previously postulated for palladium(0)-catalyzed

arylation of electron-rich heterocycles.[36] Under similar conditions, the palladium-catalyzed C3 alkynylation of indoles, was reported by Gu in 2009.[37]



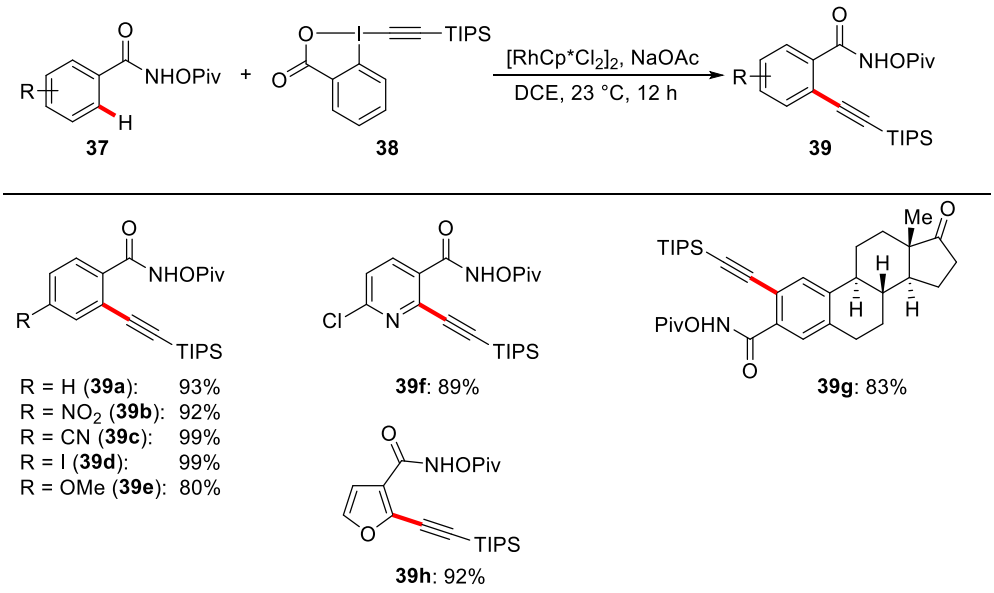
Scheme 14. Palladium-catalyzed C–H alkynylation of electron-rich heterocycles.

In 2009, the first chelation-assisted palladium-catalyzed direct C–H alkynylation of acetylanilide derivatives was reported by Chatani (Scheme 15).[38] Preliminary mechanistic studies indicated that the reaction proceeds through a pathway distinctly different from the previously reported alkynylation of electron-rich heterocycles. However, a stoichiometric amount of silver salt was necessary for this transformation, and the scope regarding the bromoalkyne component proved to be limited. Afterwards, a variety of effective C–H alkynylation protocols were established with the aid of different transition metals, such as palladium,[39] nickel,[40] rhodium,[41] iridium,[42] ruthenium,[43] copper,[44] cobalt,[45] manganese[46] and iron.[47]



Scheme 15. Palladium-catalyzed alkynylation of aromatic C–H bonds with bromoalkyne **33a**.

Meanwhile, new alkynylation reagents also emerged. In 2014, Loh reported the *ortho* C–H alkynylation of aromatic amides taking advantage of the hypervalent iodine reagent[48] **38** as the alkyne source (Scheme 16).[41f] The reaction showed high efficiency in furnishing only monoalkynylated products in excellent yields at ambient temperature. A variety of synthetically useful functional groups was well-tolerated. The synthetic utility of this protocol was illustrated by the late stage functionalization towards complex molecule **39g**.

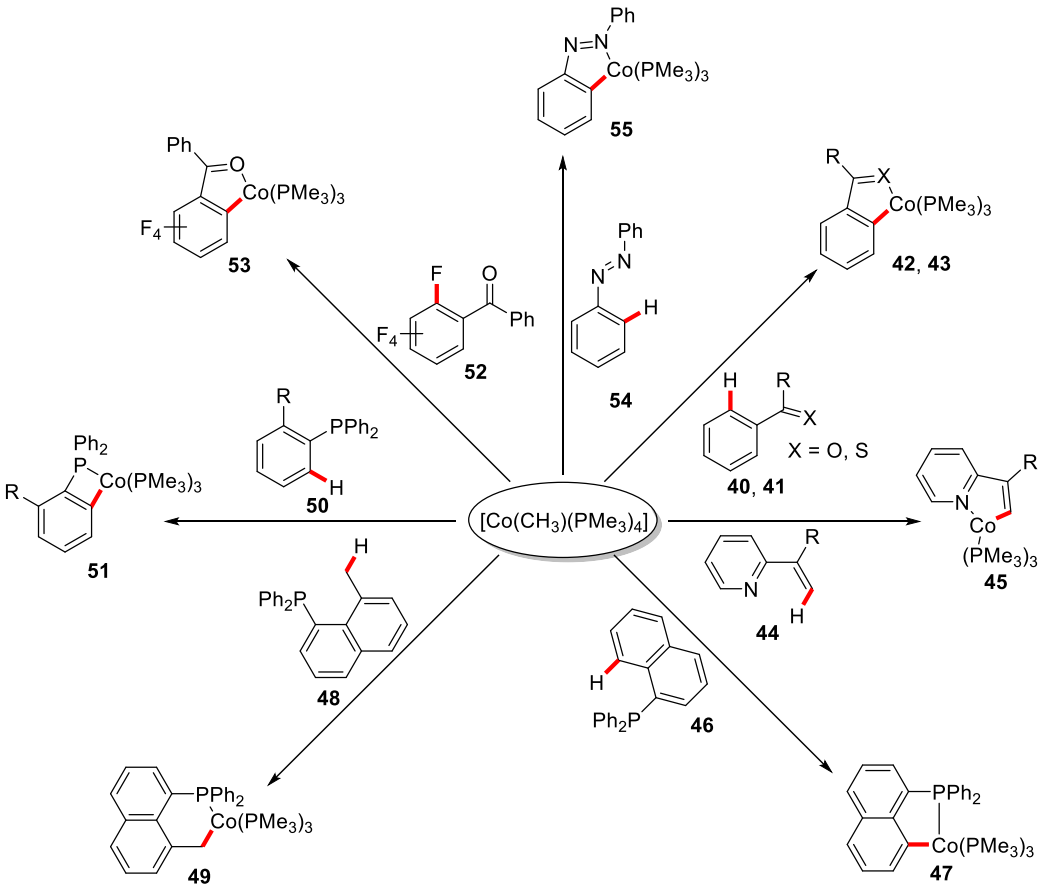


Scheme 16. Rhodium-catalyzed alkynylation of aromatic C–H bonds with the hypervalent iodine reagent **38**.

1.4 Cobalt Catalyzed C−H Functionalization

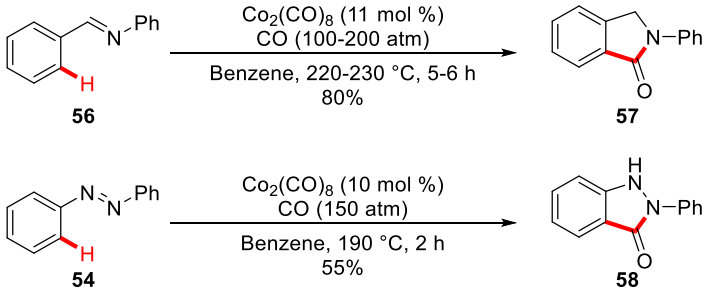
Over the past few decades, considerable progress has been achieved in transition metal-catalyzed C−H functionalization.[2a-c, 2f, 2l, 49] Until recently, most of catalyzed C−H functionalizations were realized by using expensive second- or third-row transition metals.[2c, 50] The development of catalysts based on more naturally abundant and cost-effective first row transition metal complexes, represents an attractive alternative.[2k, 51] In this context, the utilization of environmentally benign cobalt complexes bears great potential for applications to homogeneous catalysis.[52]

Given the success of precious 4d and 5d transition metals, numerous efforts have been made to explore easily accessible cobalt complexes for C−H activation.[53] As a key step of C−H cobaltation, Klein and coworkers isolated the cyclometalated cobalt complex **55** by treating azobenzene (**54**) with $[Co(CH_3)(PMe_3)_4]$.[54] Subsequently, various arenes bearing phosphorus,[55] nitrogen,[56] oxygen[57] or sulfur[58] donor groups also proved to be suitable substrates to form cyclocobaltated complexes. Indeed, the cyclometalation was not restricted to the formation of five- or six-membered cobaltacycles, but the formation of a less favourable four-membered cobaltacycle **51** was also possible (Scheme 17).



Scheme 17. Cyclocobaltated compounds by stoichiometric C−H or C−F cleavage using $[Co(CH_3)(PMe_3)_4]$.

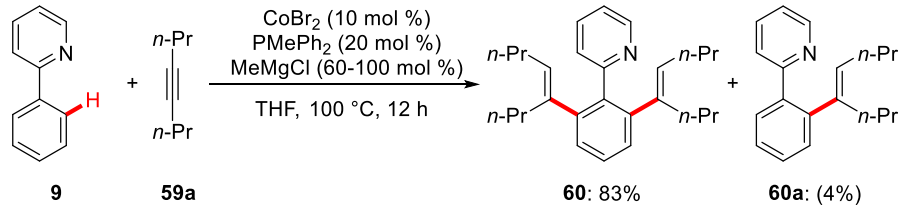
Murahashi reported the first example of a cobalt-catalyzed chelation-assisted C−H functionalization reaction. In this case, aldimine **56** or azobenzene **54** undergoes carbonylative cyclization delivering indazolone **57** or phthalimidine **58**, respectively (Scheme 18).[59] Further applications of these reactions were however limited due to harsh reaction conditions.



Scheme 18. Early examples of cobalt-catalyzed chelation-assisted C−H functionalization.

1.4.1 Low-Valent Cobalt Catalyzed C−H Activation

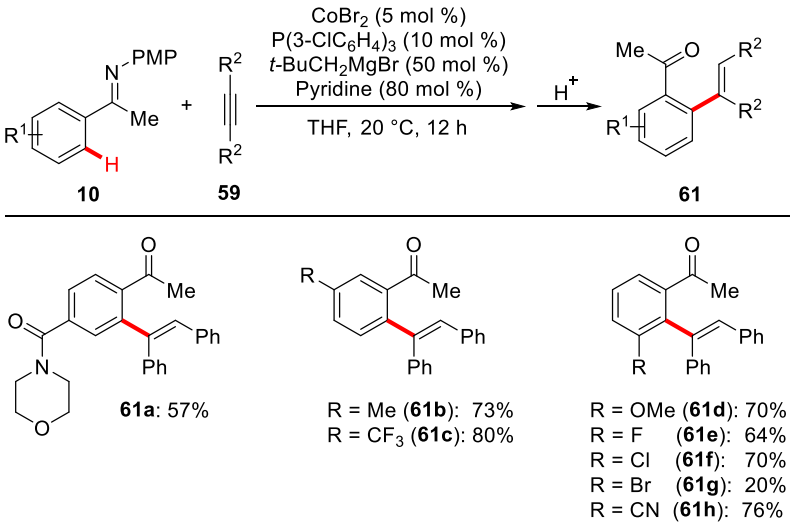
The pioneering examples of chelation-assisted C−H functionalization by low-valent cobalt catalysis were reported by Yoshikai,[53e, 53g] Nakamura[60] and Ackermann.[61] The catalytic system for these transformations usually contains a cobalt precatalyst, a ligand (such as phosphine or *N*-heterocyclic carbene (NHC)) and a Grignard reagent to generate the active low-valent cobalt species. These novel catalysts promoted a series of pyridine- and imine-directed hydroarylation reactions of alkynes and olefins at mild reaction temperatures. The combination of a cobalt−NHC catalyst and a Grignard reagent allows directed aromatic C−H functionalizations with electrophiles such as aldimines, aryl chlorides, as well as alkyl chlorides or bromides.



Scheme 19. Cobalt-catalyzed hydroarylation of alkynes **59**.

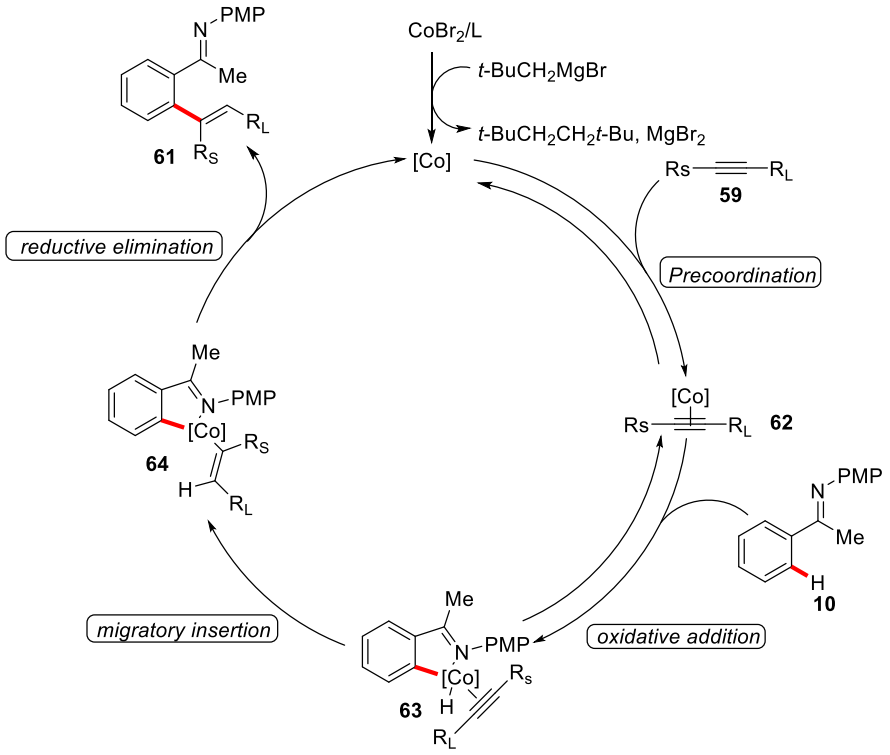
In 2010, Yoshikai and coworkers introduced a ternary catalytic system consisting of $CoBr_2$, a phosphine ligand ($PMePh_2$) and a stoichiometric reductant (MeMgCl) which efficiently catalyzed the hydroarylation of unactivated internal alkynes with arylpyridines (Scheme 19).[62] By utilizing a quaternary catalytic system consisting of a cobalt salt, a triarylphosphine ligand, a Grignard reagent, and pyridine, Yoshikai and coworkers further achieved the hydroarylation of ketimines or aldimines with unactivated internal alkynes at ambient temperature (Scheme 20).[63] A series of potentially sensitive functional groups, including chloride,

bromide, nitrile and tertiary amide, were well-tolerated. The reaction also displayed a unique regioselectivety. Thus, the presence of substituents such as methoxy, halogen, and cyano groups at the *meta*-position of the imino group led to selective C−C bond formation at the more sterically hindered C2-positions.



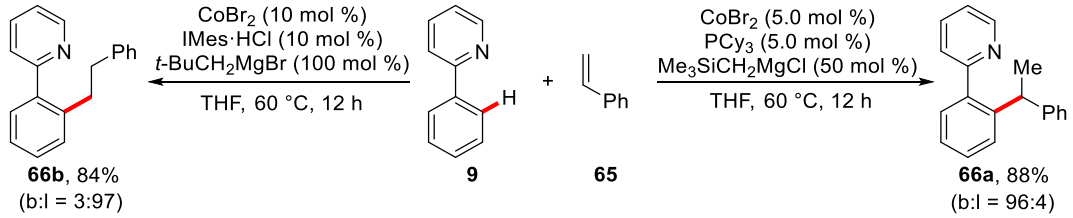
Scheme 20. Cobalt-catalyzed hydroarylation of imine **10**.

The catalytic cycle for the cobalt-catalyzed hydroarylation was proposed as follows: The active low-valent cobalt complex is generated from the cobalt(II) precatalyst and an excess *t*-BuCH$_2$MgBr (Scheme 21). Precoordination of the alkyne **59** to the active cobalt species is followed by oxidative addition into the *ortho* C−H bond of imine **10** to give cobalt complex **63**. Intramolecular hydrocobaltation of complex **63** and subsequent reductive elimination of the intermediate **64** delivers product **61** and regenerates the active cobalt species.



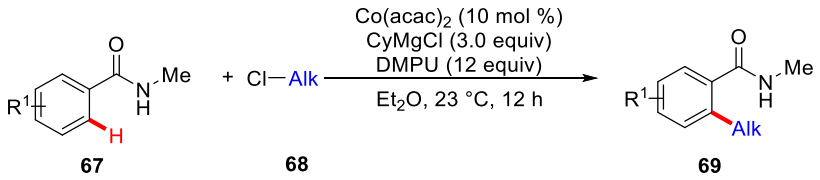
Scheme 21. Cobalt-catalyzed hydroarylation of imine **10**.

On the basis of the remarkable high efficiency of the alkyne hydroarylation,[62-64] hydroarylation of olefins also proved to be possible by utilizing low valent cobalt catalysis. In 2010, Yoshikai developed a switchable protocol for the hydroarylation of styrenes **65** giving linear or branched hydroarylation products largely by the judicious choice of either a phosphine or a *N*-heterocyclic carbene (NHC) ligand (Scheme 22).[65]



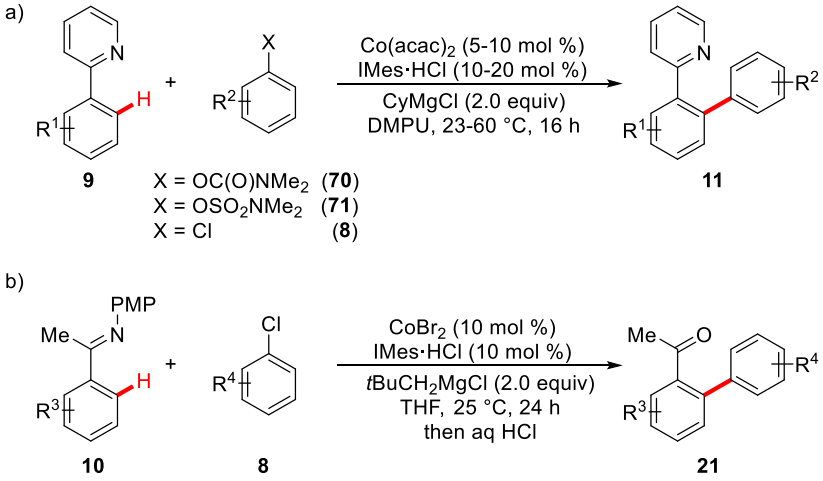
Scheme 22. Cobalt-catalyzed hydroarylation of imine **28**.

Until 2011, low valent cobalt catalysis was mainly used for addition reactions to unsaturated substrates. Nakamuru reported a cobalt-catalyzed *ortho*-alkylation protocol using alkyl chlorides as organic electrophiles (Scheme 23).[60] Here, by employing DMPU as the ligand, the alkylation of secondary benzamides was achieved with various alkyl chlorides **68**. Subsequently, arylpyridines, *N*-pyri(mi)dylindoles[61c] as well as ketimines[66] also proved to be viable substrates for this transformation by the choice of NHC preligands.



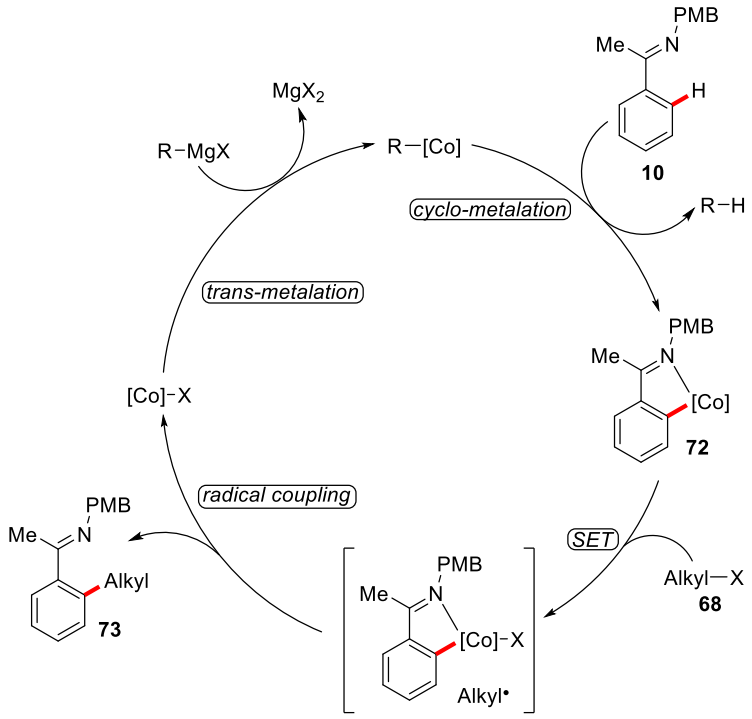
Scheme 23. Cobalt-catalyzed hydroarylation of imine **10**.

Apart from alkylations, Ackermann and coworkers showed that low valent cobalt-catalysis could be applied to the challenging C−H arylation of arenes.[61b-d] Thus, the direct arylation of arylpyridines **9** as well as 2-pyri(mi)dylindoles was accomplished with organic electrophiles, such as aryl chlorides **8**, phenol derived aryl carbamates **70** or sulfamates **71**.[61c, 67] The scope of this reaction was further extended to ketimines **10** by Yoshikai group.[68] Thus, valuable biarylketones were easily accessible after hydrolysis.



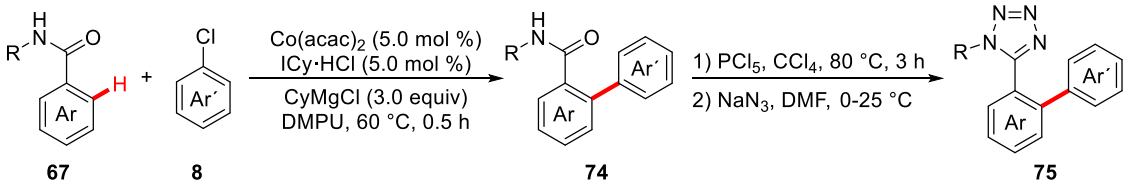
Scheme 24. Cobalt-catalyzed C−H arylations with aryl carbamates **70**, sulfamate **71** and chlorides **8**.

Mechanistic studies suggested that these transformations involve a radical intermediate. Thus, the catalytic cycle was proposed as follows (Scheme 25).[53e] First, cyclometalation of aryl imine **10** with an alkylcobalt species generated *in situ* from the cobalt precatalyst and the Grignard reagent delivers intermediate **72**. Then, single electron transfer (SET) from the cobalt center to alkyl halide **68** occurs. Finally, radical C−C coupling affords the product, and transmetalation of the resulting cobalt halide species with the Grignard reagent regenerates the alkylcobalt species.



Scheme 25. Proposed catalytic cycle for *ortho*-alkylation with alkyl halide.

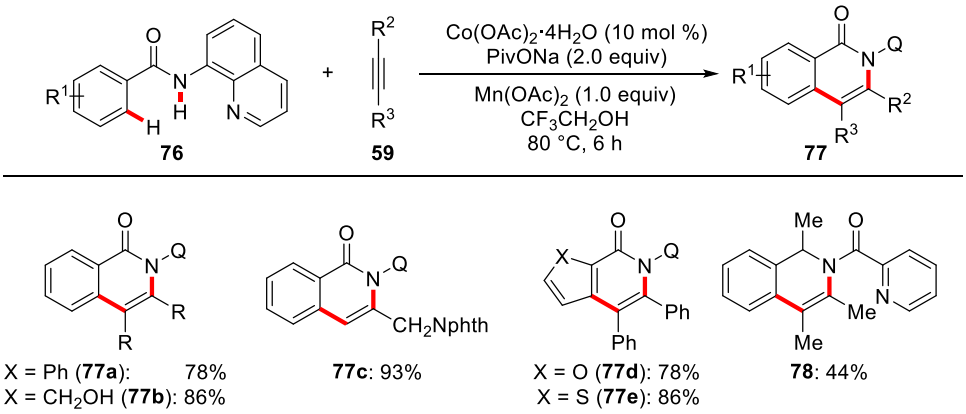
In 2015, weakly coordinating amides were also shown to be a suitable directing groups for the direct arylation by low valent cobalt catalysis.[61d] In this case, ICy·HCl (1,3-dicyclohexyl-1*H*-imidazol-3-ium chloride) (**149g**) was used as the optimal preligand. This reaction displayed a broad substrate scope for benzamides **67** as well as aryl chlorides **8**. It is noteworthy that by treating the products with PCl_5 and sodium azide, biaryl tetrazoles **75**, which are highly important building blocks in medicinal chemistry, could easily be accessed (Scheme 26).



Scheme 26. Cobalt-catalyzed C–H arylation and product diversification.

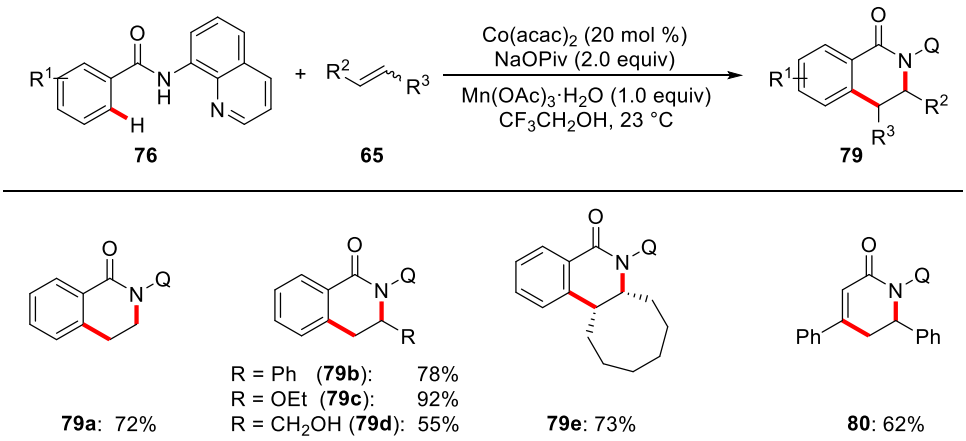
1.4.2 Cobalt-Catalyzed Oxidative C–H Activation

Since Daugulis introduced the 8-aminoquinoline auxiliary for palladium catalyzed C–H activation in 2005,[69] it became one of the most widely used and versatile directing groups in C–H functionalization chemistry.[2e, 70] In 2014, Daugulis utilized this directing group for cobalt-catalyzed oxidative alkyne annulation reactions and achieved excellent results (Scheme 28).[71] The reaction showed remarkable functional group tolerance under mild conditions, both internal and terminal alkynes were competent substrates for these transformation. The picolinamide also proved to be reactive under the same conditions, albeit with diminished yield.



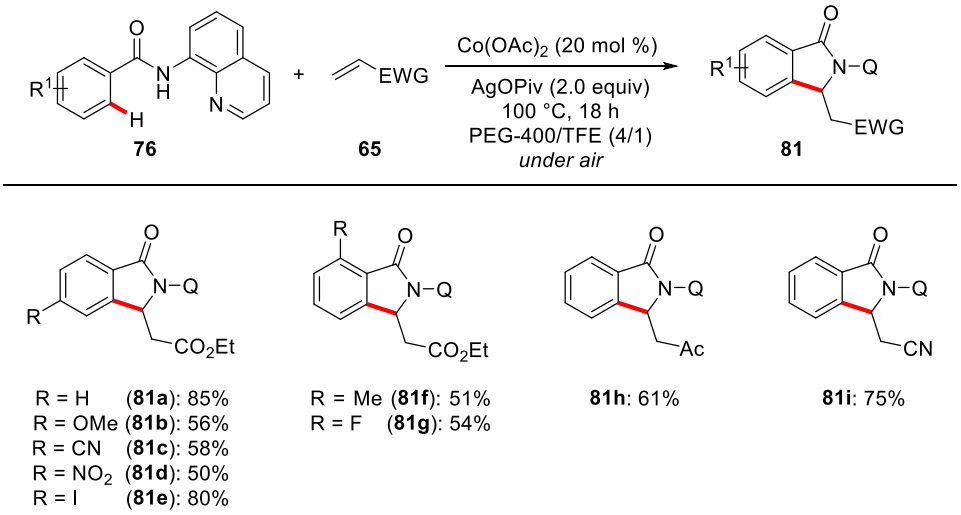
Scheme 27. Cobalt-catalyzed C–H annulations by 8-aminoquinoline auxiliaries.

Utilizing a similar catalytic system, Daugulis and coworkers further achieved the hydroarylation of unactivated alkenes (Scheme 28).[72] Thus, a series of dihydroisoquinolinone derivatives was obtained step-economically at ambient temperature. Subsequently, the cobalt-catalyzed or promoted- direct carbonylation[73] and dimerization[74] were also shown to be possible.



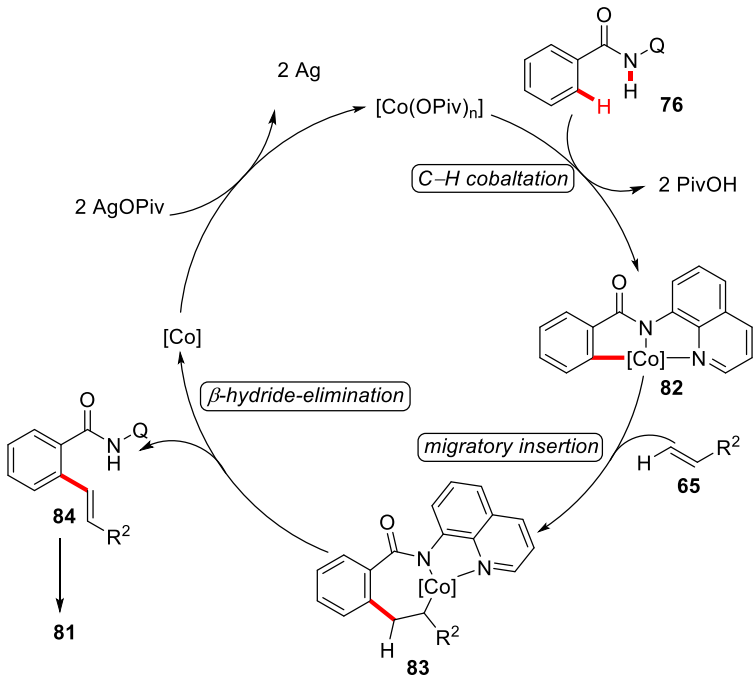
Scheme 28. Cobalt-catalyzed hydroarylation of unactivated alkenes.

Another interesting result in this field was reported by Ackermann and coworkers. They identified a complementary oxidative coupling reaction with electron-deficient olefins that provides expedient access to synthetically useful isoindolin-1-ones (Scheme 29).[75] A wide range of functional groups, such as methoxy, halogen, cyano or even nitro substituents, were well tolerated.



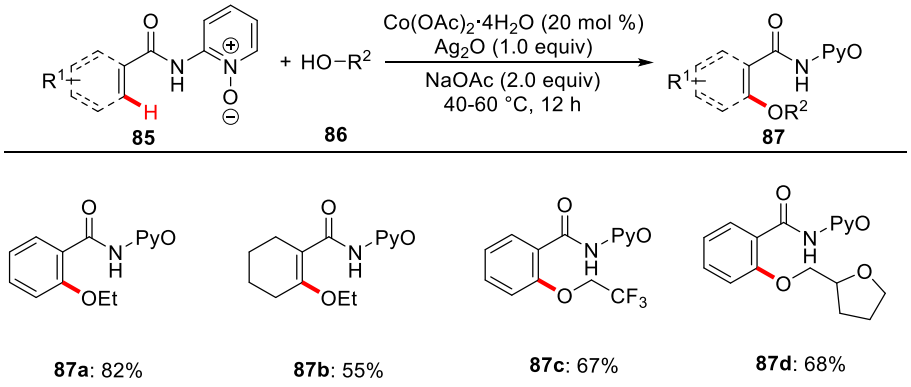
Scheme 29. Cobalt-catalyzed isoindolinone synthesis.

A possible catalytic cycle was proposed as follows: The oxidative alkene annulation proceeds *via* a kinetically relevant, carboxylate-assisted C−H cobaltation. Subsequent migratory insertion of the olefin **65**, followed by *β*-hydride-elimination, delivers the alkenylated benzamide **84**, which finally undergoes an intramolecular alkene hydroamidation to furnish the desired isoindolinones **81** (Scheme 30).



Scheme 30. Proposed catalytic cycle for cobalt-catalyzed isoindolinone synthesis.

In 2014, Song and coworkers employed 2-aminopyridine-1-oxide (PyO) as a removable *N*,*O*-bidentate-type directing group in copper-mediated direct aryloxylation of benzamides.[76] Later, this directing group was utilized in cobalt catalyzed C(sp^2)–H alkoxylation reactions (Scheme 31).[77] The reaction proceeded under mild conditions using inexpensive $Co(OAc)_2 \cdot 4H_2O$ as the catalyst. However, a stoichiometric amount of silver oxide was required as oxidant in this transformation.



Scheme 31. Cobalt-catalyzed C–H alkoxylation.

1.4.3 High Valent Cobalt(III)-Catalyzed C−H Activation

In recent years, C−H activation using Cp*Rh(III) catalysts has underwent an remarkable development. [2c, 2i, 50e, 78] A variety of C−C and C−heteroatom bond-forming reactions by means of C−H activation have been achieved in both oxidative and redox-neutral manners. Although Cp*Rh(III)-catalyzed processes are useful and versatile, the need for expensive and precious rhodium sources is economically and environmentally disadvantageous. In this context, researchers have focused on the development of mild and cost-effective catalysts.[2k, 51, 79]

In 2013, Matsunaga, Kanai, and co-workers disclosed a major breakthrough in the analogous Cp*Co(III) catalysis, identifying a cationic Co(III) complex, $[Cp^*Co(C_6H_6)(PF_6)_2]$, as a competent catalyst for the addition of 2-arylpyridines to *N*-sulfonylimines and enones *via* a C−H activation process (Scheme 32).[80] Among several cyclopentadienyl–cobalt(III) complexes (Figure 2), the [Cp*Co-(benzene)] complex (**88**) showed the highest activity. The reason could be that this complex showed the best balance between reactivity and stability.

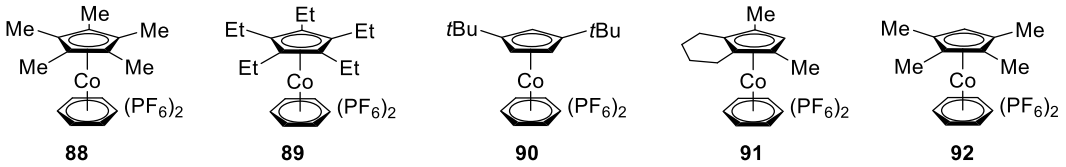
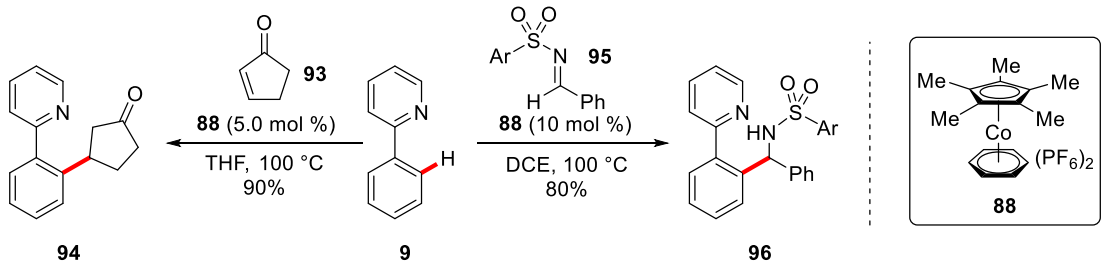
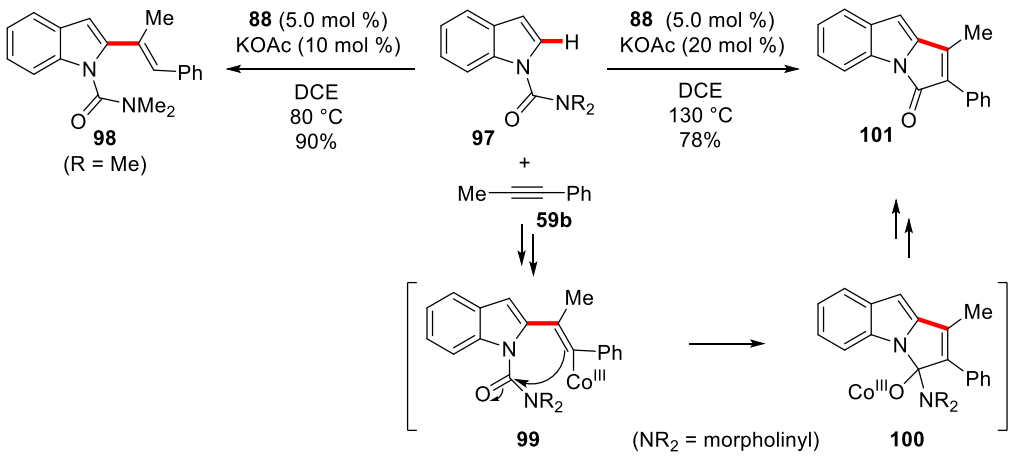


Figure 2. Structure of cationic high-valent cyclopentadienyl cobalt(III) complexes.



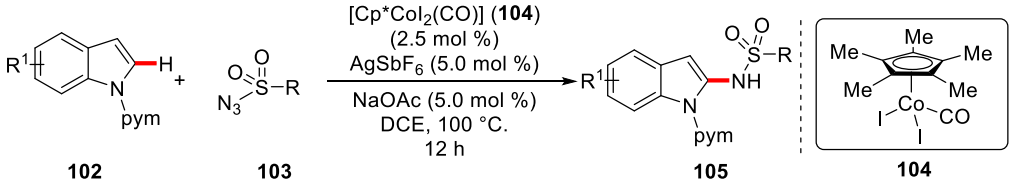
Scheme 32. Addition of 2-arylpyridines to *N*-sulfonyladimines or *α,β*-unsaturated ketones.

Complex **88** also showed a unique reactivity in the reaction of *N*-carbamoylindole with an internal alkyne.[81] A C2-selective indole alkenylation/annulation sequence proceeded smoothly with catalytic amounts of cobalt(III) complex **88** and KOAc. By tuning the carbamoyl group and the reaction conditions, the product selectivity can be easily controlled to deliver either alkenylation or annulation products (Scheme 33). Interestingly, when Cp*Rh(III) complexes were used, only the alkenylation product was formed. This clear difference highlighted the unique nucleophilic nature of the organocobalt species.



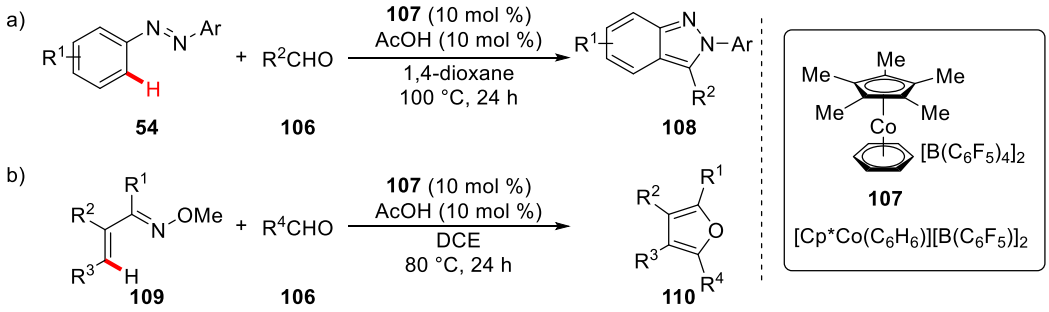
Scheme 33. Reaction of *N*-carbamoylindole **97** and alkyne **59b** leading to pyrrolo-indolone **101** or 2-alkenylindole **98**.

In an effort to expand the scope of Cp*Co(III) catalysis, Kanai successfully applied the bench-stable [Cp*CoI_2(CO)] complex **104**, which was first prepared by Li and Jin as early as 2004,[82] for the C2-selective C−H amidation of indole **102** (Scheme 34).[83] This *in situ* generated Cp*Co(III) catalyst showed significant potential for C−H functionalization and attracted an increasing attention in the past few years.



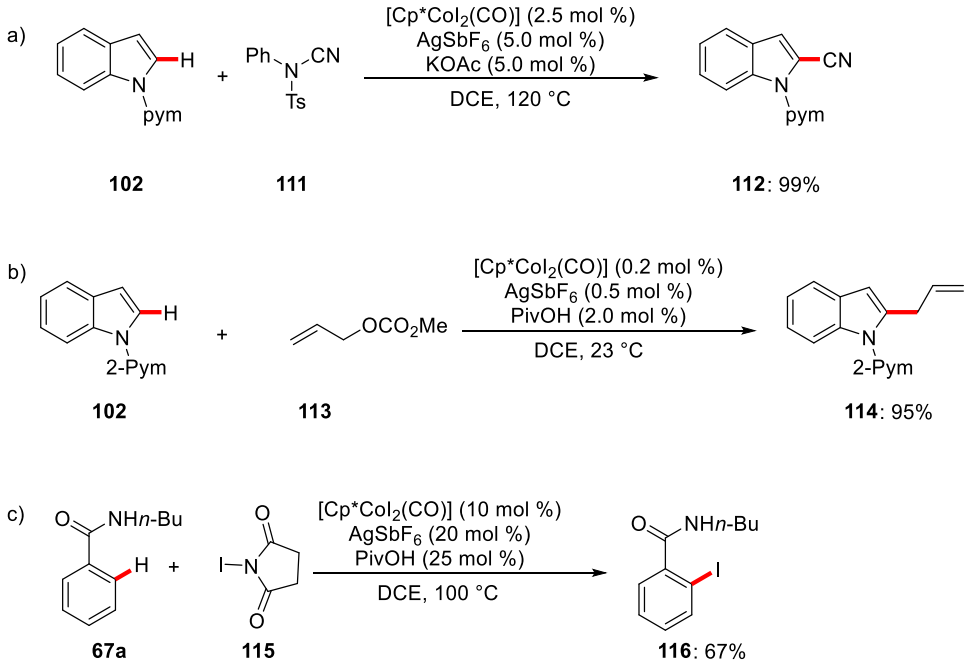
Scheme 34. Cobalt-catalyzed C2 selective amidation of indoles.

It is well known that Cp*Co(III)-catalyzed reactions easily proceed *via* cyclocobaltation and addition onto multiple bonds. These addition reactions were mainly restricted to alkynes and conjugated double bonds. However, Ellman disclosed a cobalt-catalyzed addition of C−H bonds to carbonyl compounds.[84] Thus, azobenzenes **54** as well as *α,β*-unsaturated oximes **109** were efficiently transformed into indazoles **108** or furans **110,** respectively, *via* insertion of aromatic aldehydes **106** and trapping of the thus-formed alcohols by nucleophilic attack (Scheme 35).



Scheme 35. Condensation of azobenzene or *α,β*-unsaturated oximes with aldehyde **106**.

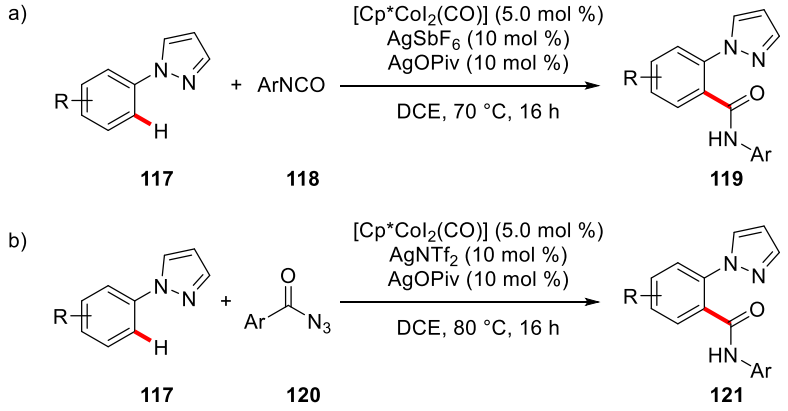
In 2015, the Ackermann group reported the first example of cobalt-catalyzed direct C−H cyanations of 2-arylpyridines, *N*-pyrimidylindoles and related (hetero)arenes by utilizing the readily available *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) as cyanating reagent (Scheme 36a).[85] Thereafter, Glorius and co-workers also achieved C−H cyanation under similar conditions in an independent study.[86] The scope of Cp*Co(III)-catalysis was further extended to C−H allylations and halogenations by using pivalic acid instead of acetate salt as a key catalyst component (Scheme 36 b and c).[87] It is noteworthy that both the silver and the carboxylate additive were crucial for these transformations, presumably for the generation of a cationic Co(III) carboxylate species.



Scheme 36. Cobalt-catalyzed C−H cyanation, iodination and allylation.

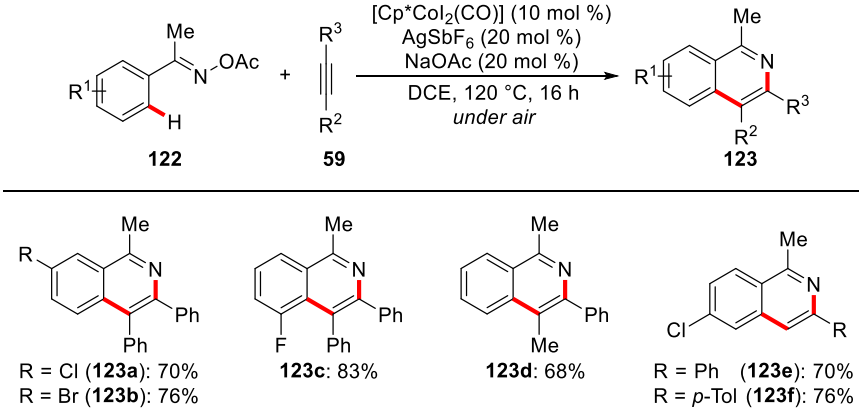
Ackermann and co-worker developed the first cobalt(III)-catalyzed aminocarbonylation of aryl pyrazoles **117** (Scheme 37).[88] The aminocarbonylation with isocyanates **118** as the electrophiles gave optimal results with

[Cp*Co(CO)I_2] (**104**) as the precatalyst, along with $AgSbF_6$ and AgOPiv as the additives. The reaction showed high functional group tolerance and remarkable site selectivity with *meta*-substituted arenes **117**. As isocyanates could be generated *in situ* from acyl azides *via* a Curtius rearrangement, acyl azides **120** could also be used as suitable coupling partners.[2g, 89] A similar transformation was also reported by Ellman subsequently.[90]



Scheme 37. Cobalt(III)-catalyzed aminocarbonylation of aryl pyrazole **117**.

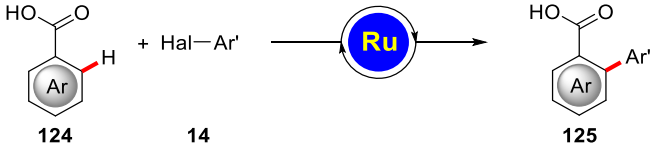
The isoquinoline framework is an important structural motif found in a series of biologically active natural products and pharmaceuticals.[91] In 2015, a cobalt(III)-catalyzed C−H/N−O functionalizations for the redox-neutral preparation of isoquinolines **123** was reported by the Ackermann,[92] Kanai[93] and Sundararaju[94] research groups independently (Scheme 38). Although annulation reactions of oxime derivatives **122** and alkynes **59** by C−H activation to give isoquinolines **123** without the use of any external oxidants have been developed using various transition metal catalysts, the substrate scope was however limited to internal alkynes in all the previous reports.[95] Notably, the Cp*Co(III)-catalyst exhibited much higher site selectivity for *meta*-substituted *O*-acyl oximes and higher reactivity towards terminal alkynes than the Cp*Rh(III) catalyst.



Scheme 38. Cobalt(III)-catalyzed C−H/N−O functionalization.

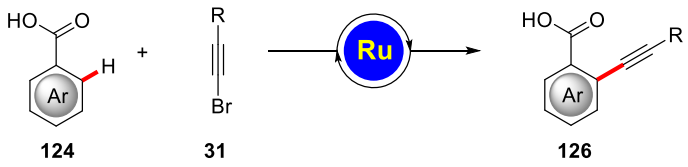
2 Objectives

Biaryls are core structural motifs in biologically active compounds, which are of great importance for the agrochemical and pharmaceutical industries.[11] Transformations of unactivated C−H bonds have emerged as an attractive alternative to conventional cross-coupling approaches, enabling step-economical biaryl syntheses with minimal byproduct formation.[13] Major advances have been accomplished by means of ruthenium(II)-catalyzed reactions with easily accessible electrophilic aryl halides.[2f, 28-29, 29d, 96] Despite these undisputable advances, ruthenium(II)-catalyzed C−H arylations with organic electrophiles are limited to strongly coordinating nitrogen-containing directing groups, which are difficult to remove or modify. [29d, 97] Therefore, the development of ruthenium(II)-catalyzed C−H arylations of weakly-*O*-coordinating[98] benzoic acids is highly desirable (Scheme 39).



Scheme 39. Ruthenium(II)-catalyzed C–H arylation by weakly coordinating benzoic acids.

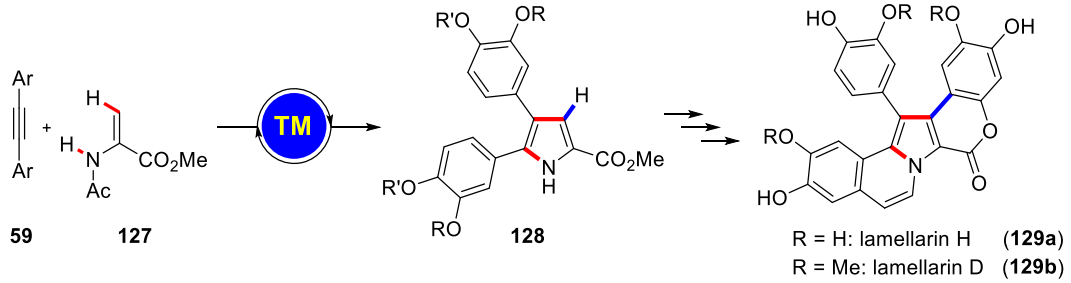
Arylalkynes are versatile building blocks in organic synthesis. As a consequence, the development of efficient strategies for the construction of alkynes is an important goal, often being achieved by the conventional Sonogashira–Hagihara cross-coupling reaction.[32] Recently, transition metal-catalyzed C−H functionalization has emerged as a powerful alternative for the direct introduction of alkynyl moieties.[25, 30a, 40a, 44-47] Despite this undisputable progress, ruthenium-catalyzed C–H alkynylations of weakly-*O*-coordinating substrates have proven elusive.[43] In consideration of the unique synthetic utility of substituted alkynes, we thus became attracted to devise an unprecedented ruthenium(II)-catalyzed C−H alkynylation of weakly-*O*-coordinating benzoic acids (Scheme 40).



Scheme 40. Ruthenium(II)-catalyzed C–H alkynylation by weakly coordinating benzoic acids.

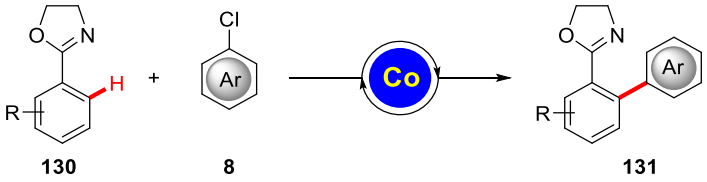
The past decade has witnessed the emergence of C–H activation as an increasingly powerful tool in natural product synthesis,[99] with considerable recent progress being achieved by versatile ruthenium(II) catalysts. In 2013, Ackermann and coworkers reported a versatile pyrrole synthesis through ruthenium(II)-catalyzed oxidative C–H/N–H functionalizations.[100] In continuation of these studies, and given the antibiotic, anti-cancer and anti-malaria activities of pyrrole-containing lamellarin alkaloids,[101] it was therefore one goal of

this work to conduct a comparative study on the performance of various transition metal catalysts in the preparation of naturally-occurring lamellarins **129** (Scheme 41).



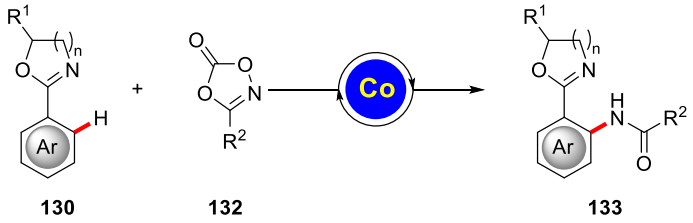
Scheme 41. Ruthenium(II)-catalyzed C–H/N–H activation for the assembly of lamellarin alkaloids.

In consideration of the natural abundance and low costs of 3d transition metals, the focus in catalytic C–H activation has shifted in the recent years towards the use of base metal catalysis, with major advances accomplished by versatile cobalt catalysts.[2k, 51, 79] In this context, Ackermann[61b-d] and Yoshikai[68, 102] have achieved C–H arylations with organic halides by the use of low-valent cobalt catalysis. Recently, the functionalization of otherwise unreactive C–H bonds in oxazolines has gained interest,[20e, 25, 103] as modified oxazolines were found to exhibit biological activity.[104] Hence, studying cobalt-catalyzed C–H arylation of oxazolines by a modifiable directing group[105] strategy was an important target of this thesis (Scheme 42).



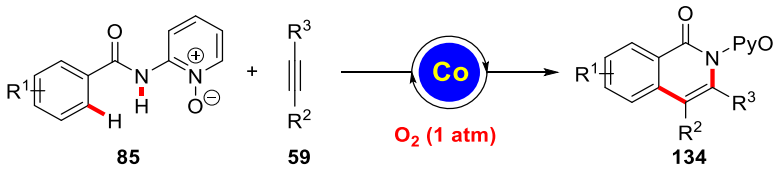
Scheme 42. Cobalt-catalyzed C–H arylation by oxazoline assistance.

Substituted oxazolines are omnipresent structural motifs of numerous bioactive compounds of relevance to crop protection and medicinal chemistry.[106] As a consequence, there is a continued strong demand for flexible methods that provide general access to substituted oxazolines. So far, catalytic C−H amidations on aryl oxazolines are restricted to the use of precious rhodium and iridium catalysts, as elegantly developed by Chang, among others.[107] Therefore, it is of great significance to develop a new versatile protocol for cobalt(III)-catalyzed C−H amidations of synthetically useful aryl oxazolines by the action of dioxazolones as user-friendly amidating reagents (Scheme 43).



Scheme 43. Cobalt-catalyzed oxazolinyl-assisted C−H amidation.

Although remarkable progress has been achieved with low-valent cobalt catalysis, these catalytic systems usually require sub-stoichiometric or stoichiometric amounts of Grignard reagents as the reductant and the base.[53d-g] Therefore, a variety of valuable functional groups were not tolerated under these reaction conditions, which represents a major drawback. In this context, Daugulis,[71-72] Ackermann[108] and Song[109] developed the oxidative cobalt-catalyzed alkyne and alkene annulation reactions. Based on these considerable recent advances, we set out to develop the first general protocol by cobalt oxidase-type reactions with molecular oxygen as the sole oxidant (Scheme 44).



Scheme 44. Cobalt-catalyzed oxidase C−H functionalization.

3 Results and Discussion

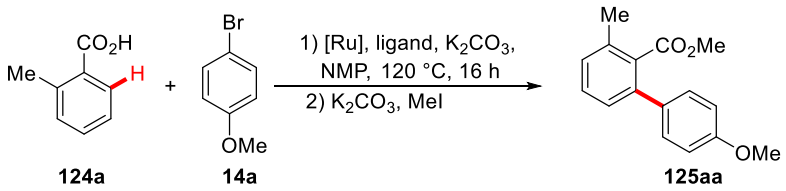
3.1 Ruthenium(II)-Catalyzed C–H Functionalizations on Benzoic Acids with Aryl and Alkenyl Halides by Weak-*O*-Coordination

Biaryls are ubiquitous in natural products, pharmaceuticals, agrochemicals, ligands, polymers and organic materials.[10-12] Recently, direct arylation of otherwise inert C–H bonds has emerged as an attractive alternative to conventional cross-coupling strategies, enabling the regiospecific introduction of aryl groups in unfunctionalized positions.[13] However, this great conceptual advantage is often offset by the structural complexity of the required directing groups. Only recently, various functional groups with low coordinating ability,[97, 110] such as carboxylates, have successfully been used as directing groups for *ortho* C–H arylations.[111] The key benefit of carboxylate groups is that they can be tracelessly removed by protodecarboxylation or utilized as leaving groups in a rapidly growing number of decarboxylative coupling reactions.[112] As a result, we started to explore the possibility of developing unprecedented C−H arylations of benzoic acids by reasonably priced ruthenium(II) catalyst.

3.1.1 Optimization Studies

We initiated our studies by testing a series of different ligands for the envisioned ruthenium(II)-catalyzed C–H arylation of weakly *O*-coordinating benzoic acids **124a** (Table 2). The typical *N*-heterocyclic carbene precursors (entries 2–3) or SPO (entries 4–7) ligands were not effective in providing access to arylated benzoic acid product **125aa**. To our delight, moderate conversion was obtained when PPh_3 was employed (entries 8–14). The yield could be further improved to 81% when the PCy_3 ligand was used (entry 14). The control experiments showed that there was no reaction in the absence of ruthenium catalyst or K_2CO_3 (entries 15-16). The aryl chlorides **8** proved to be unreactive under the current conditions (entry 17). It is noteworthy that the well-defined [$RuCl_2(PCy_3)$(*p*-cymene)] was also identified as a user-friendly single component catalyst, allowing for the preparation of the *ortho*-arylated benzoic acid **125aa** with comparable levels of efficiency (entry 18). The catalytic performance was further improved by exploiting carboxylate assistance with the aid of the well-defined ruthenium(II)biscarboxylate complex **16** (entry 19). Probing different solvents revealed DMA to be suitable, but provided lower yield of the desired product (entries 20-22).

Table 2. Optimization study for ruthenium (II)-catalyzed C–H arylation.[a]



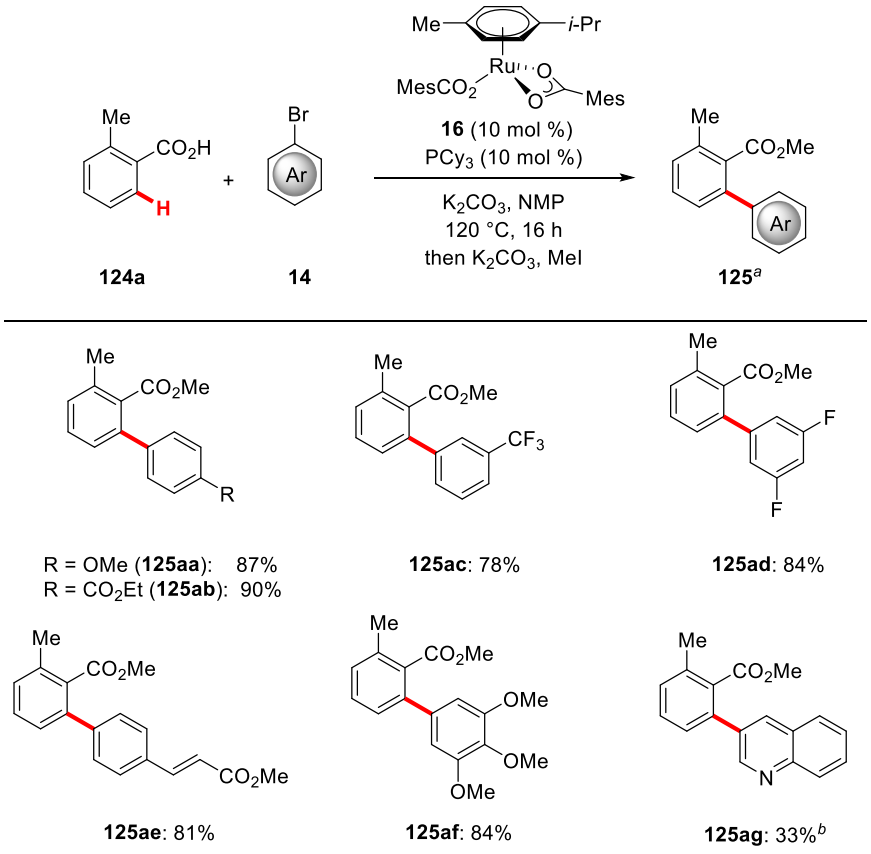
entry	[Ru]	ligand	**125aa** (%)[b]
1	$[RuCl_2(p\text{-cymene})]_2$	---	(11)
2	$[RuCl_2(p\text{-cymene})]_2$	IPr·HCl	(<5)
3	$[RuCl_2(p\text{-cymene})]_2$	IMes·HCl	(<5)
4	$[RuCl_2(p\text{-cymene})]_2$	$t\text{Bu}_2\text{POH}$	16
5	$[RuCl_2(p\text{-cymene})]_2$	Cy_2POH	(<5)
6	$[RuCl_2(p\text{-cymene})(\text{Ph}t\text{BuPOH})]$	---	(<5)
7	$[RuCl_2(p\text{-cymene})(n\text{Bu}_2\text{POH})]$	---	(6)
8	$[Ru(O_2CMes)_2(p\text{-cymene})]$	X-Phos	(7)
9	$[RuCl_2(p\text{-cymene})]_2$	DavePhos	(<5)
10	$[RuCl_2(p\text{-cymene})]_2$	JohnPhos	(8)
11	$[RuCl_2(p\text{-cymene})]_2$	P(*n*-Bu)(Adamantyl)$_2$	20
12	$[RuCl_2(p\text{-cymene})]_2$	P(*t*-Bu)$_3$	(22)
13	$[RuCl_2(p\text{-cymene})]_2$	PPh_3	(51)
14	$[RuCl_2(p\text{-cymene})]_2$	PCy_3	81
15[c]	$[RuCl_2(p\text{-cymene})]_2$	PCy_3	n.d.
16	---	PCy_3	n.d.
17[d]	$[RuCl_2(p\text{-cymene})]_2$	PCy_3	(5)
18	$[RuCl_2(p\text{-cymene})(PCy_3)]$	---	75
19	**$[Ru(O_2CMes)_2(p\text{-cymene})]$ (16)**	**PCy_3**	**87**
20[e]	$[Ru(O_2CMes)_2(p\text{-cymene})]$ (**16**)	PCy_3	54
21[f]	$[Ru(O_2CMes)_2(p\text{-cymene})]$ (**16**)	PCy_3	n.d.
22[g]	$[Ru(O_2CMes)_2(p\text{-cymene})]$ (**16**)	PCy_3	(32)

[a] Reaction conditions: **124a** (0.50 mmol), **14a** (0.75 mmol), [Ru] (10 mol %), ligand (10 mol %), K_2CO_3 (2.0 equiv), and NMP (2.0 mL), 120 ºC, 16 h. [b] Yields of isolated product; in parentheses: GC conversion after esterification with K_2CO_3 (2.0 equiv) and MeI (5.0 equiv) in MeCN (3.0 mL) with 1,3,5-trimethoxybezene as internal standard. [c] Without K_2CO_3. [d] Using 4-chloroanisole **8a** instead of 4-bromoanisole **14a**. [e] DMA (2.0 mL) as solvent. [f] PhMe (2.0 mL) as solvent. [g] DMPU (2.0 mL) as solvent.

3.1.2 Scope of Ruthenium(II)-Catalyzed C–H Arylation

3.1.2.1 Scope of Aryl Bromides in the Ruthenium(II)-Catalyzed C–H Arylation

With the optimized catalytic system in hand, we tested its versatility in the C–H arylation of differently substituted aryl bromides **2** (Scheme 45). Here, a representative set of synthetically useful functional groups, such as halides, activated alkenes and esters were well tolerated by the optimized catalyst at *para* or *meta* positions of the aryl electrophiles. Moreover, electron-deficient as well as typically more demanding electron-rich aryl halides **14** were efficiently converted. Even the heterocyclic substrate 3-bromoquinoline **14g** gave moderate yield of the corresponding product.

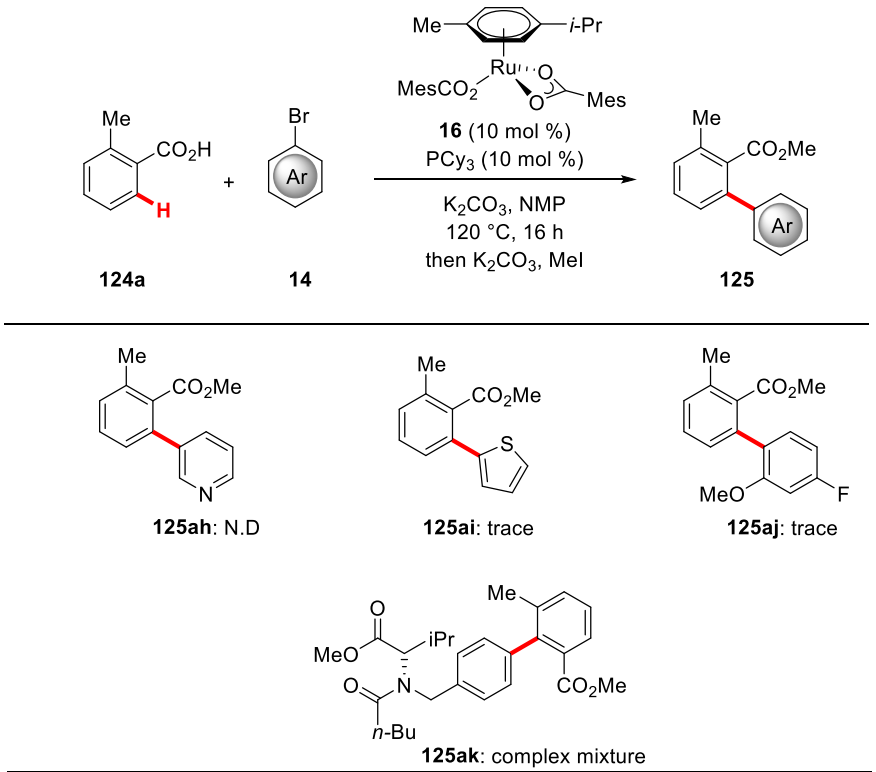


[a] Reaction conditions: **124a** (0.50 mmol), **14** (0.75 mmol), **16** (10 mol %), PCy_3 (10 mol %), K_2CO_3 (2.0 equiv), and NMP (2.0 mL), 120 °C, 16 h. [b] NaI (2.0 equiv) was used as additive.

Scheme 45. Scope of aryl bromides in the ruthenium(II)-catalyzed C–H arylation.

However, some substrates also turned out to be incompatible with the current catalytic conditions (Scheme 46). Typical heterocycles, such as 3-bromopyridine **14h** and 2-bromothiophene **14i**, were unreactive. The sterically hindered *ortho* substituted aryl bromide **14j** proved unsuitable as well under the current condition. Moreover,

aryl bromide **14k**, which is functionalized with a chiral tertiary amide moiety, gave unsatisfactory result, delivering a complex mixture of unidentified products.

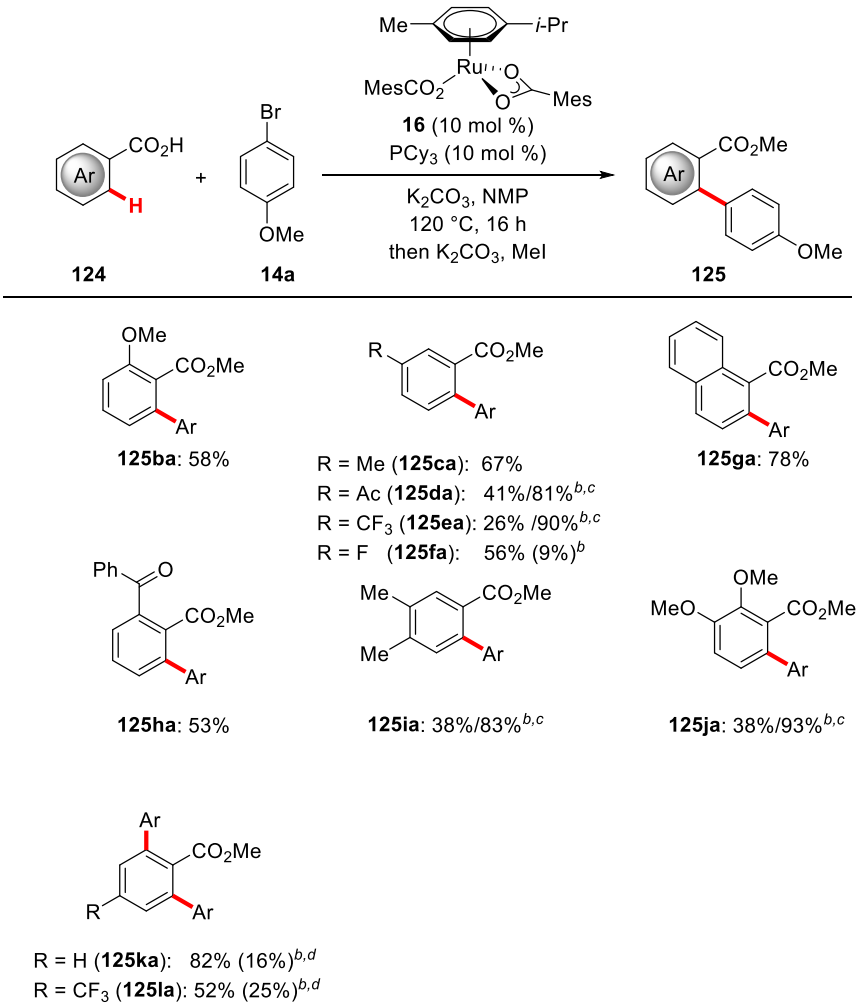


[a] Reaction conditions: **124a** (0.50 mmol), **14** (0.75 mmol), **16** (10 mol %), PCy_3 (10 mol %), K_2CO_3 (2.0 equiv), and NMP (2.0 mL), 120 °C, 16 h.

Scheme 46. Limitations of the ruthenium(II)-catalyzed C–H arylation with regard to aryl bromides.

3.1.2.2 Scope of Benzoic Acids

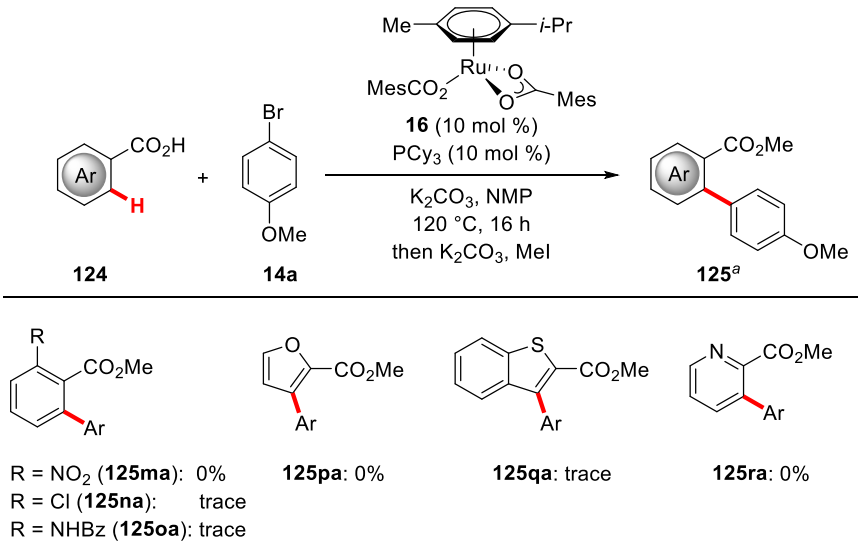
Subsequently, we explored the scope of viable benzoic acids in the ruthenium(II)-catalyzed C–H arylation reaction (Scheme 47). Thus, various weakly-coordinating benzoic acids **124** could be converted with high catalytic efficiency and excellent positional selectivity by the phosphine-modified biscarboxylate complex **16**. Although in some cases (**124d-e, 124i-j**) only moderate yield could be obtained, to our delight, the yields could be improved to an excellent level when aryl iodide **14a´** was employed instead of aryl bromide **14a**.



[a] Reaction conditions: **124a** (0.50 mmol), **14a** (0.75 mmol), **16** (10 mol %), PCy_3 (10 mol %), K_2CO_3 (2.0 equiv), and NMP (2.0 mL), 120 °C, 16 h. [b] using ArI. [c] Performed by Cuiju Zhu. [d] Using ArI **14a´** (3.0 equiv), yields of diarylated products were in parenthesis.

Scheme 47. Scope of the ruthenium(II)-catalyzed C–H arylation with regard to benzoic acid **124**.[a]

Benzoic acid **124m** containing a strong electron-withdrawing nitro group, unfortunately delivered no product. Also the *ortho* choloro- or benzamide-substituted substrates **124n-o** were unreactive and failed to provide the desired products. Heterocyclic benzoic acids, such as furan, thiophene or pyridine, were so far incompatible with the current catalytic conditions (**124p-r**) (Scheme 48).

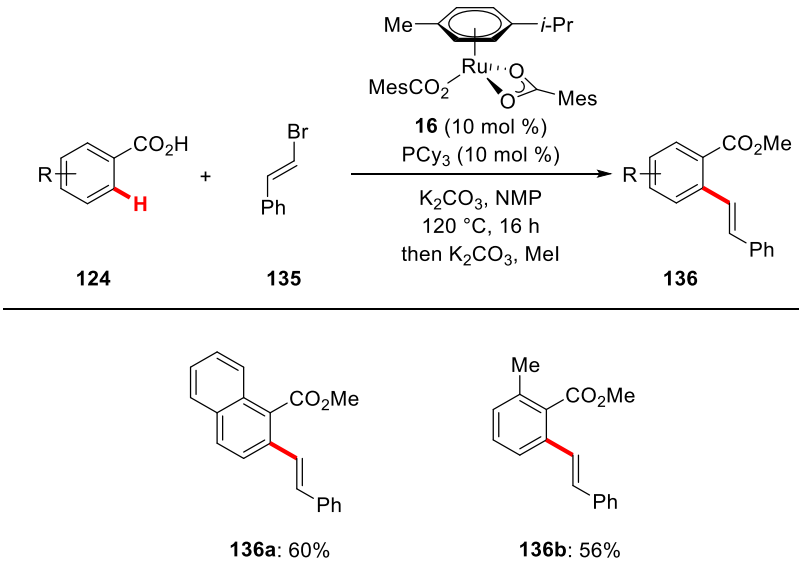


[a] Reaction conditions: **124** (0.50 mmol), **14a** (0.75 mmol), **16** (10 mol %), PCy_3 (10 mol %), K_2CO_3 (2.0 equiv), and NMP (2.0 mL), 120 °C, 16 h.

Scheme 48. Challenging benzoic acids **124** in the ruthenium(II)-catalyzed C–H Arylation.

3.1.3 Weak *O*-Coordination for C–H Alkenylation

To our delight, the unique utility of our ruthenium(II) catalysis was further demonstrated by enabling the olefination of benzoic acid **124** with alkenyl halide **135** (Scheme 49). Thus, a series of *ortho* alkenylated benzoic acid derivatives were easily accessible.

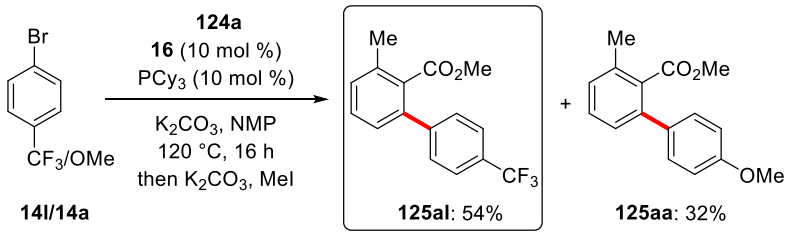


Scheme 49. Weak *O*-coordination for C–H alkenylation.

3.1.4 Mechanistic Studies

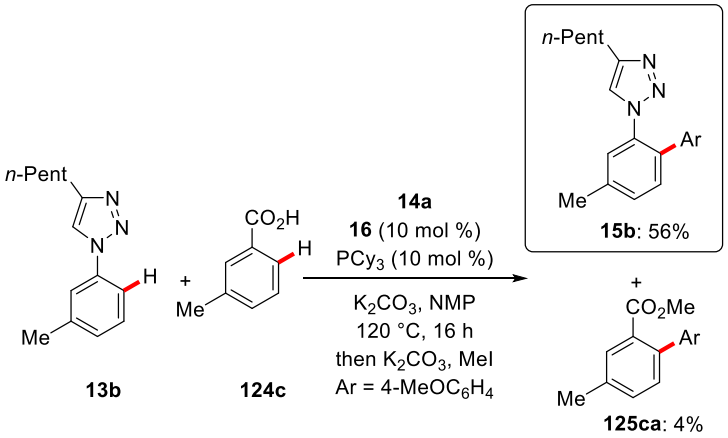
3.1.4.1 Intermolecular Competition Experiments

In consideration of the unique efficiency of the ruthenium(II) catalysis regime, we performed a series of experiments to rationalize its mode of action. Intermolecular competition experiments between aryl bromides **14l** and **14a** revealed the electron-deficient aryl bromide **14l** to be inherently more reactive (Scheme 50).



Scheme 50. Intermolecular competition experiment between aryl bromides **14l** and **14a**.

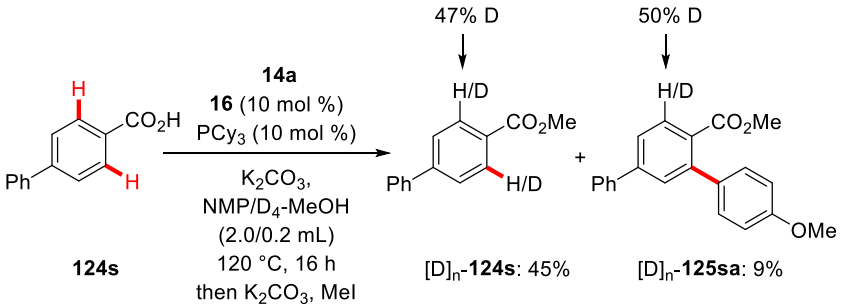
We further performed an intermolecular competition experiment between benzoic acid **124c** and strongly coordinating triazole **13b** (Scheme 51). It turned out that the strongly *N*-coordinating 1,2,3-triazole[113] substrate **13b** reacted preferentially. This result further demonstrated the challenging nature of the C–H arylation with weakly coordinating benzoic acids **124**.



Scheme 51. Competition experiment between benzoic acid **124c** and triazole **13b**.

3.1.4.2. C–H Arylation in the Presence of Isotopically Labelled Cosolvent

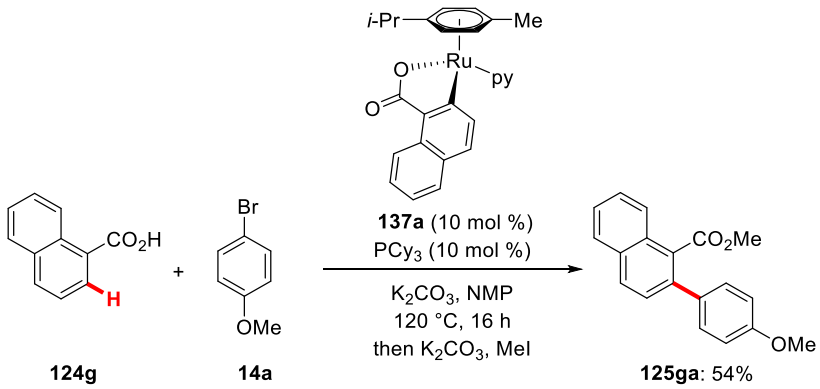
Moreover, a significant H/D scrambling upon the addition of an isotopically labelled cosolvent under otherwise identical reaction conditions was observed. This finding showed that the C–H metalation is most likely reversible (Scheme 52).



Scheme 52. Facile C–H arylation in the presence of isotopically labelled cosolvent.

3.1.4 3. Ruthenacycle for C–H Arylation

Additionally, we prepared the potential intermediate ruthenacycle **137a**, which was previously employed for oxidative alkyne annulations by Ackermann and coworkers.[114] Notably, the cyclometalated complex **137a** showed a similar activity compared to catalyst **16** and afforded the corresponding arylation product **125ga** in moderate yield (Scheme 53). This result indicated that the cyclometalated complex **137a** could be a key intermediate for this transformation**.**

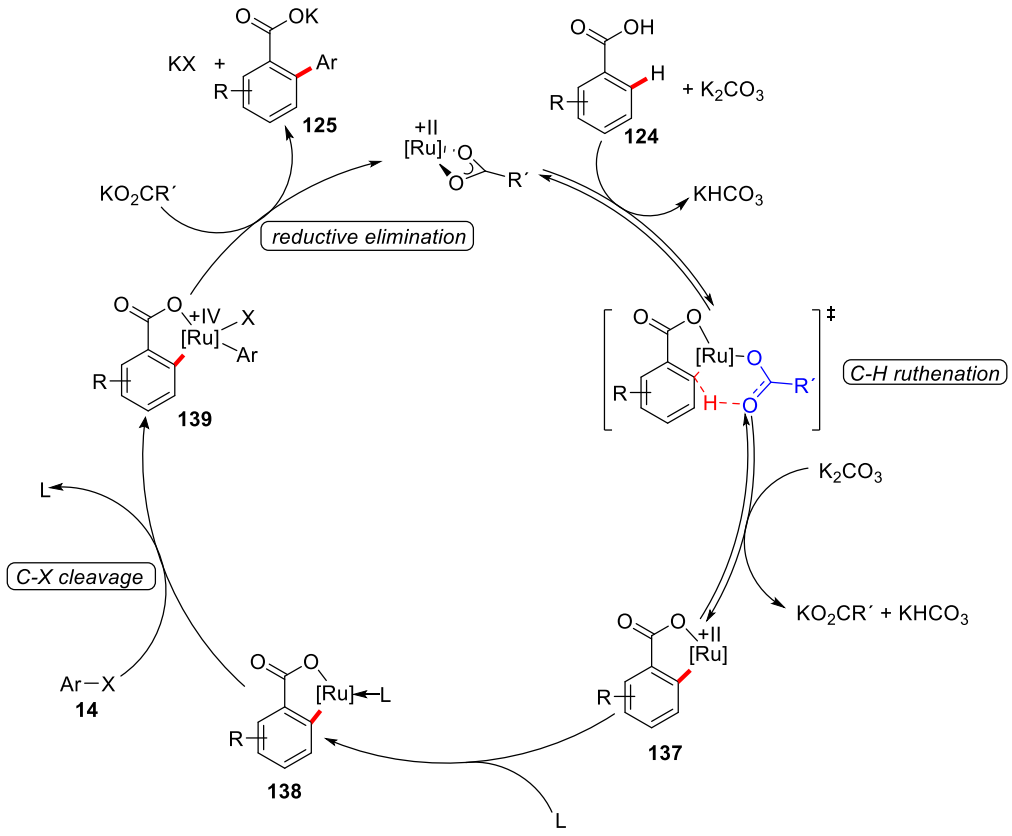


Scheme 53. Ruthenacycle **137a** as catalyst in the C–H arylation.

3.1.4.4 Proposed Catalytic Cycle

Based on these mechanistic studies, we proposed a plausible catalytic cycle for this arylation protocol. First, the initial C–H bond activation enables a reversible carboxylate-assisted cycloruthenation of benzoic acid **124**

to form ruthenacycle **137**, which then undergoes an oxidative addition with the assistance of electron-rich phosphine ligand PCy_3.[115] Finally, reductive elimination of **139** releases the arylated product **125** and regenerates the active ruthenium catalyst (Scheme 54).



Scheme 54. Plausible catalytic cycle for benzoic acid-directed C–H arylation.

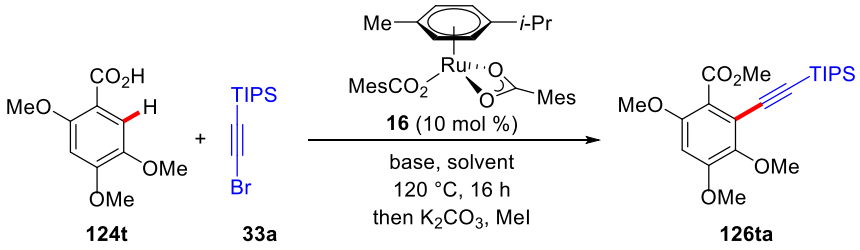
3.2 Ruthenium(II)-Catalyzed C−H Alkynylation of Weakly-Coordinating Benzoic Acids

In recent years, robust ruthenium(II) carboxylate catalysis has proven particularly powerful for redox-neutral C−H transformations with organic electrophiles.[2f, 116] Despite these considerable advances, ruthenium-catalyzed C–H alkynylations of weakly-*O*-coordinating benzoic acids have proven elusive.[43] In consideration of the unique synthetic utility of substituted alkynes, [41f, 45-47] one part of this thesis focused on the development of ruthenium(II)-catalyzed C−H alkynylation of weakly-*O*-coordinating benzoic acids.

3.2.1 Optimization Studies for Ruthenium(II)-Catalyzed C−H Alkynylation

We initiated our studies by probing various reaction conditions for the envisioned C−H alkynylation of weakly coordinating benzoic acid **124t** with bromoalkyne **33a** using the single-component ruthenium(II) biscarboxylate catalyst **16** (Table 3). Among a variety of bases, the weak base K_2CO_3 proved to be optimal (entries 1−6). No product was observed when the carboxylate-free complex [$RuCl_2$(*p*-cymene)] was used in combination with $AgSbF_6$ as the additive (entry 7). The presence of typical phosphine ligand did not improve the catalytic efficiency (entry 8). Then, the solvent effect was tested and 1,4-dioxane was shown to be the most suitable solvent for this transformation. The desired C−H alkynylation also proceeded when the corresponding alkynyl chlorides **33a´** or iodides **33a´´** were employed, albeit with lower yields (entries 16 and 17).

Table 3. Optimization of ruthenium(II)-catalyzed C–H alkynylation with benzoic acid **124t**.[a]



124t **33a** **126ta**

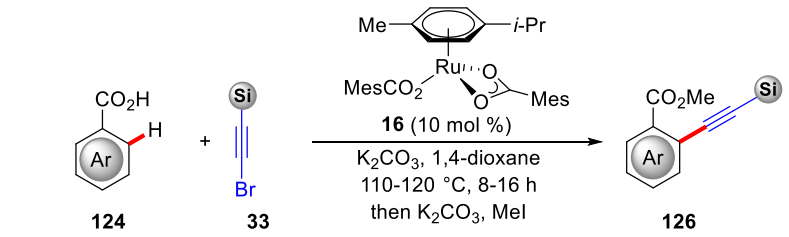
entry	base	solvent	**126ta** (%)[b]
1	K_2CO_3	NMP	63
2	$NHCy_2$	NMP	55
3	DBU	NMP	(47)
4	$NaHCO_3$	NMP	47
5	KOAc	NMP	(22)
6	K_3PO_4	NMP	33

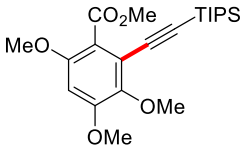
7	K_2CO_3	NMP	---[c]
8	K_2CO_3	NMP	46[d]
9	K_2CO_3	DMA	(52)
10	K_2CO_3	DMF	72
11	K_2CO_3	DMPU	(57)
12	K_2CO_3	GVL	(47)
13	**K_2CO_3**	**1,4-Dioxane**	**88**
14	K_2CO_3	CH_3CN	85
15	K_2CO_3	PhMe	53
16	K_2CO_3	1,4-Dioxane	39[e]
17	K_2CO_3	1,4-Dioxane	24[f]

[a] Reaction conditions: **124t** (0.50 mmol), **33a** (0.65 mmol), **16** (10 mol %), Base (2.0 equiv), Solvent (1.0 mL), 120 °C, 16 h; then K_2CO_3 (2.0 equiv) and MeI (5.0 equiv) in MeCN (3.0 mL). [b] Yields of isolated products; in parentheses: ^{1}H-NMR conversion after esterification with 1,3,5-trimethoxybezene as the internal standard. [c] $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (20 mol %); [d] 10 mol % Xphos as additive; [e] Using alkynyl chloride **33a´**; [f] Using alkynyl iodine **33a´´**.

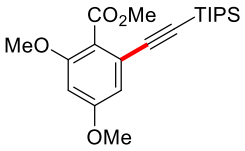
3.2.2 Scope of C–H Alkynylation by Weak Coordination

With the optimized reaction conditions in hand, we explored its versatility in the ruthenium(II)-biscarboxylate-catalyzed C−H alkynylation with weakly coordinating benzoic acids **124** (Scheme 55). Thus, the utility of the ruthenium(II)-catalyzed C−H activation was demonstrated by tolerating electron-rich as well as electron-deficient benzoic acids **124**. A variety of synthetically useful functional groups, including ether, fluoro, chloro, bromo and ketone, were well accepted. Notably, not only the TIPS substituted alkyne **31a** was a viable substrate, but also the TBDMS substituted alkyne **31b** could be transformed to the corresponding product **126jb** in synthetically meaningful yield. The current strategy allowed the double alkylynation for substrates **124k, 124z** and **124aa** being devoid of *ortho* substituent. Thus, a series of fully substituted aryl alkynes were synthesised efficiently (**126za-126aaa**). For substrate **124d** bearing a bulky acetyl group at the *meta* position the alkynylation took place at the sterically less hindered position.

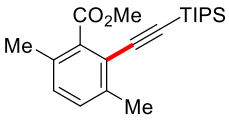




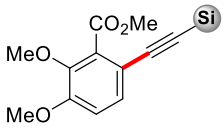
126ta: 88%



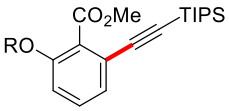
126ua: 76%



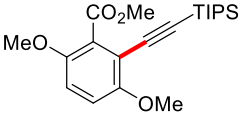
126va: 75%



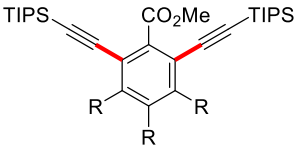
Si = TIPS (**126ja**): 82%
Si = TBDMS (**126jb**): 67%
Si = TBS (**126jc**): 26%



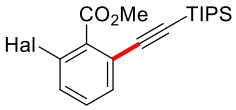
R = Me (**126ba**): 78%
R = Et (**126wa**): 76%
R = Ph (**126xa**): 79%



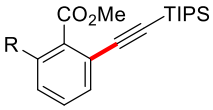
126ya: 92%



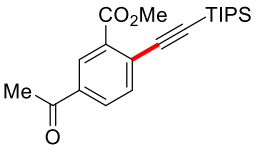
R = H (**126ka**): 58%
R =F (**126za**): 84%
R = OMe (**126aaa**): 91%



Hal = F (**126aba**): 76%
Hal = Cl (**126na**): 73%
Hal = Br (**126aca**): 52%



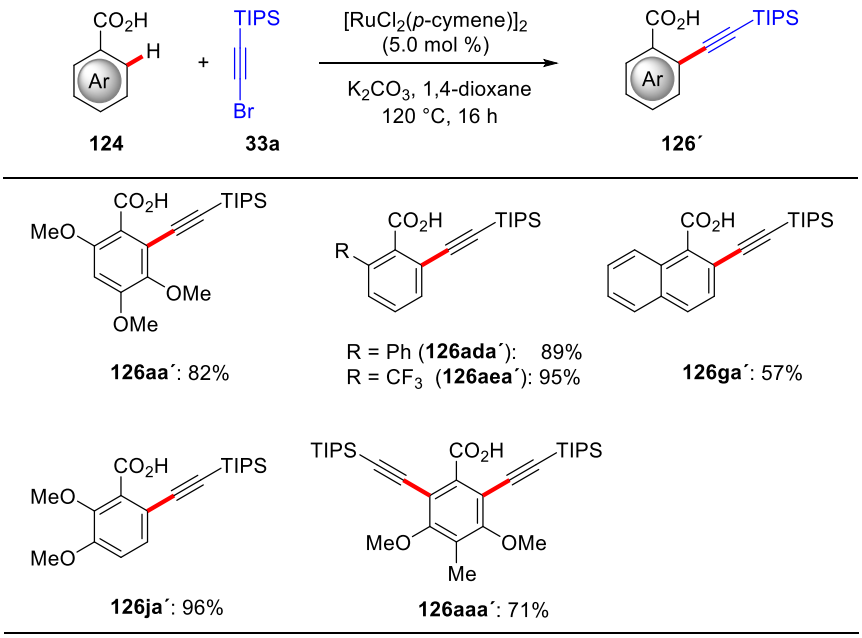
R = Ph (**126ada**): 64%
R = CF_3 (**126aea**): 69%



126da: 40%

Scheme 55. Scope of C–H alkynylation by weak coordination.

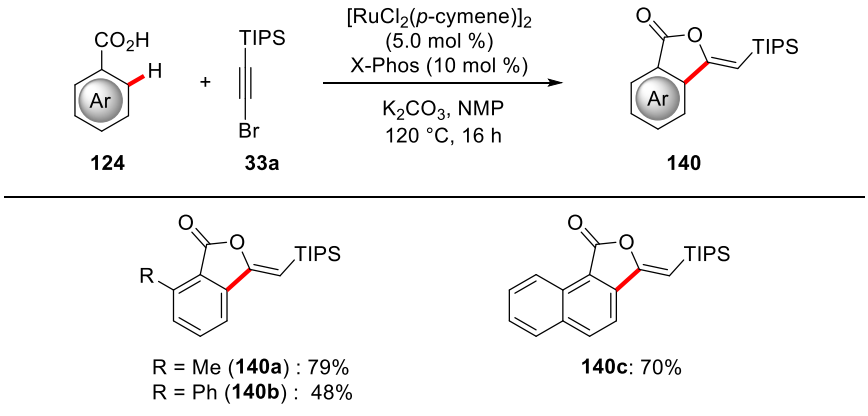
The synthetic impact of this methodology was further demonstrated by the facile preparation of a series of *ortho*-alkynylated free benzoic acid derivatives **126´**(Scheme 56).



Scheme 56. Scope of C–H alkynylation of free benzoic acids **124** by weak coordination.

3.2.3 C−H Alkynylation/Cyclization Cascade

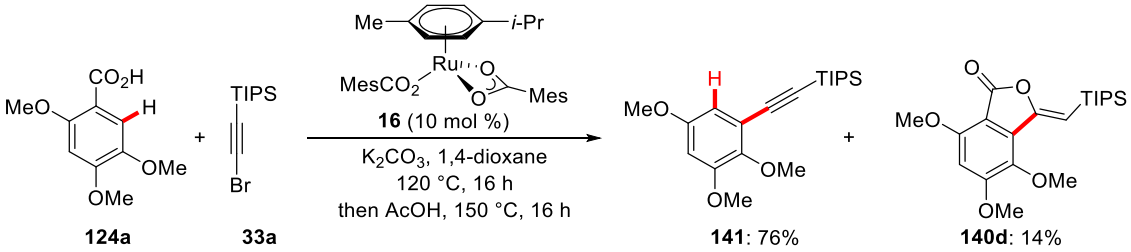
The versatility of the ruthenium(II) catalysis manifold was highlighted by a C−H alkynylation/addition sequence of substrates **124** and **33a** in the presence of the X-Phos ligand (Scheme 57). Thus, the exo-methylene phthalides **140a-c** were obtained with high yields in a step-economical manner.



Scheme 57. C−H Alkynylation/cyclization cascade.

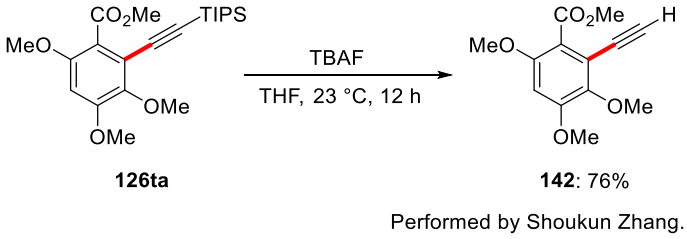
3.2.4 Product Diversivications

Finally, we uncovered an unprecedented decarboxylative C−H alkynylation to assemble the *meta*-alkynylated arene **141** (Scheme 58). Importantly, the decarboxylative *ortho*-C−H alkynylation proved viable in the absence of copper(I) or silver(I) additives, which were typically required for decarboxylative palladium- or rhodium-catalyzed transformations in previous reports.[112a, 112b, 117]



Scheme 58. Decarboxylative C−H alkynylation.

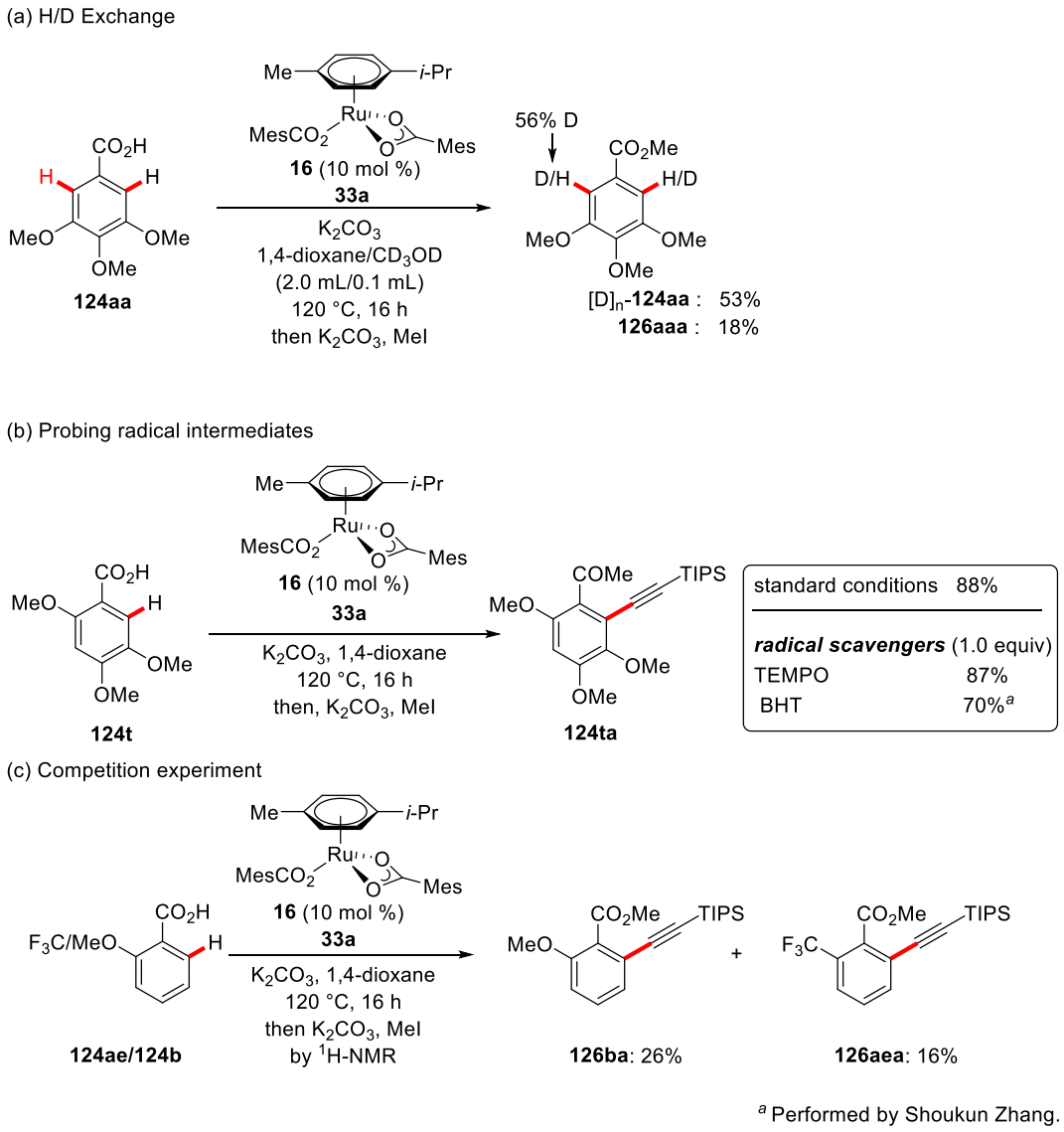
The synthetic utility of the ruthenium(II)-catalyzed C−H alkynylation was reflected by the facile removal of the silyl-group under mild reaction condition (Scheme 59). As a result, further transformations, such as Sonogashira–Hagihara cross-coupling,[32] azide-alkyne cycloaddition,[118] are to be easily realized.



Scheme 59. Removal of silyl-group.

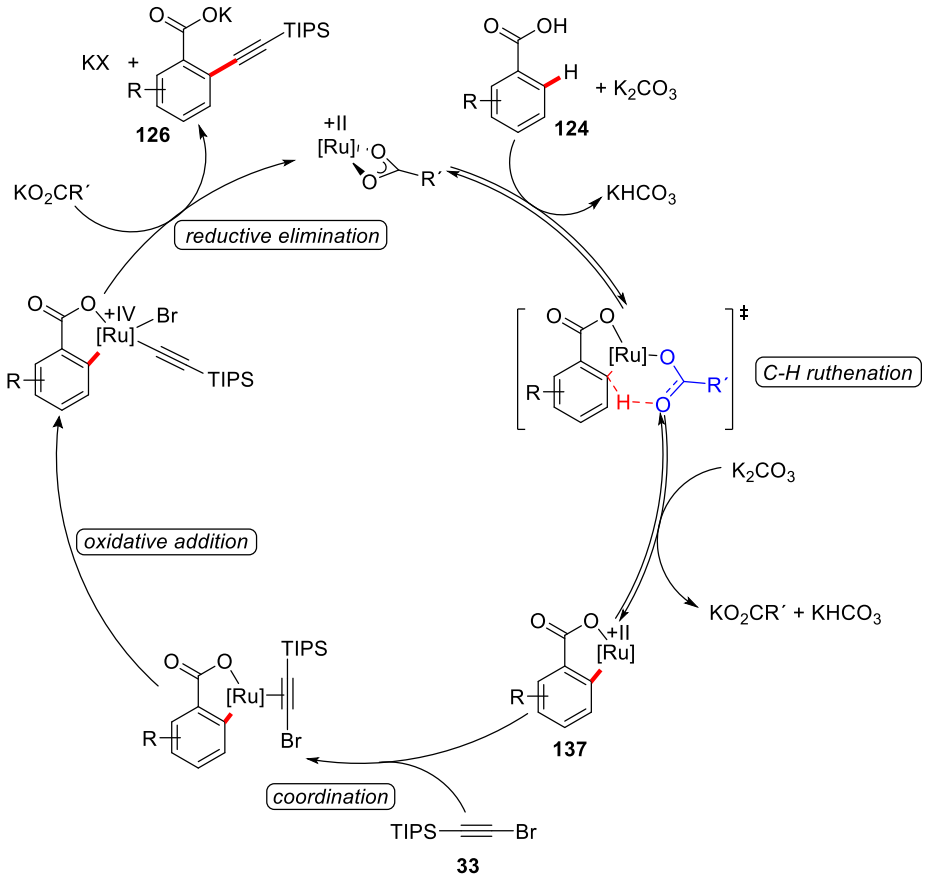
3.2.5 Mechanistic Studies

A set of experiments towards elucidation of the mechanistic aspects were performed. First, C−H alkynylation was performed in the presence of the isotopically labelled cosolvent CD_3OD. A significant H/D exchange could be observed in the reisolated substrate $[D]_n$-**124aa**. This result can be rationalized in terms of a reversible carboxylate-assisted C−H activation (Scheme 60a). Furthermore, the introduction of stoichiometric amounts of typical radical scavengers did not significantly decrease the efficacy of the C−H alkynylation, which indicates that a radical mechanism is unlikely (Scheme 60b). Moreover, an intermolecular competition experiment showed electron-rich aryl bromide to be preferentially converted (Scheme 60c). This outcome could be rationalized by a facile base-assisted internal electrophilic substitution-type (BIES) C−H activation.



Scheme 60. Mechanistic studies of ruthenium-catalyzed C−H alkynylation.

Based on these mechanistic studies, a plausible catalytic cycle was proposed as follow: First, the initial C–H bond activation involves a reversible carboxylate-assisted cycloruthenation of carboxylic acid **124** to form ruthenacycle **137**, which was then coordinated by the TIPS alkyne. Subsequent oxidative addition and reductive elimination forms the desired product and regenerates the active ruthenium(II) catalyst (Scheme 61).



Scheme 61. Proposed catalytic cycle for ruthenium-catalyzed C−H alkynylations.

3.3 Concise Synthesis of Lamellarin Alkaloids by C–H/N–H Activation

Lamellarins are polycyclic marine alkaloids that contain a central pyrrole moiety (Figure 3).[119] Since the first discovery of lamellarins A−D from *Lamellaria* sp. by Faulkner and co-workers in 1985,[120] more than 50 lamellarins have been isolated from various marine organisms.[119, 121]

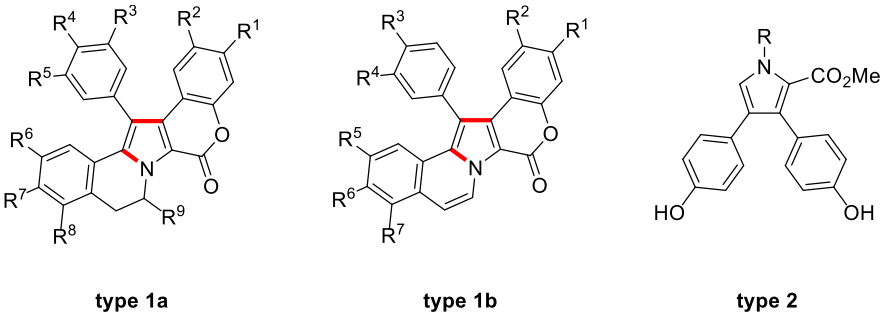
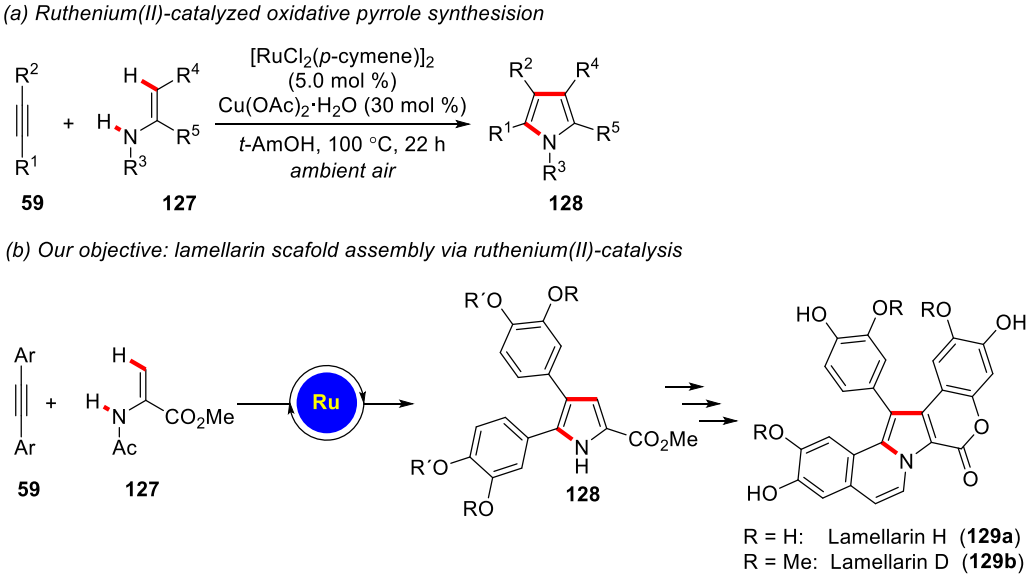


Figure 3. Structure of lamelarins type **1a**, **1b** and **2**.

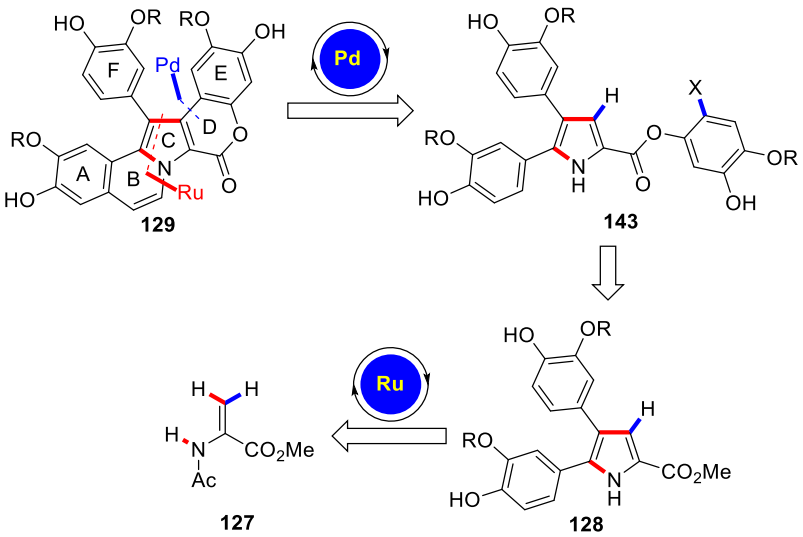
Given the antibiotic, anti-cancer and anti-malaria activities of pyrrole-containing lamellarin alkaloids,[101a-f, 101h] various synthetic routes for the preparation of lamellarins have been developed.[122] These syntheses basically can be classified into two major categories; one utilizes ring-formation reactions using appropriately substituted acyclic precursors, while the other employs the functionalization of preexisting pyrroles.[123] In 2013, Ackermann and cowockers reported a versatile ruthenium(II) catalyzed oxidative C–H/N–H functionalization of enamides (Scheme 62a).[100] This strategy set the stage for a step-economical pyrrole synthesis. In continuation of this study, we became attracted to conduct a step-economical lamellarin alkaloid synthesis (Scheme 62b).



Scheme 62. Ruthenium(II)-catalyzed C–H/N–H activation for the assembly of lamellarin alkaloids.

3.3.1 Retrosynthetic Analysis

Our studies were inspired by identifying pyrrole **143** as the key intermediate for a C–H activation-based lamellarin synthesis. Starting from the diaryl-substituted pyrrole **128** which derived from the metal-catalyzed C–H/N–H activation strategy, the annelation of the D-ring can be achieved by Suzuki-Miyaura coupling and intramolecular esterification. Finally, the construction of the B-ring could be accomplished by a two-step Pomeranz−Fritsch-type cyclization[122c, 122e, 122g] protocol (Scheme 63).

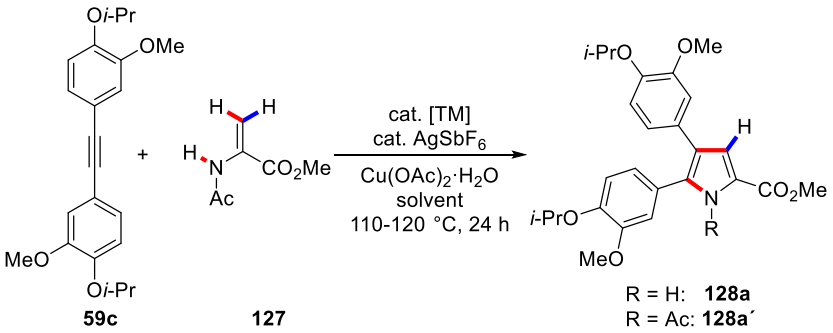


Scheme 63. Retrosynthetic analysis for lamellarin alkaloids **4**.

3.3.2 Optimization for the Preparation of Key Intermediate 128a

We initiated our studies by testing the efficiency of different transition metal complexes[100, 124] in the envisioned C–H/N–H functionalization of enamides **127** with alkyne **59c** (Table 4). The desired products were not observed in the absence of typical transition metal catalysts (entry 1). However, trace amounts of products **128** were detected when cobalt(III) complexes[124a, 124b] or $Pd(OAc)_2$[124c, 124d] were used as the catalyst (entries 2 and 4). In contrast, rhodium(III)[124g] and less expensive ruthenium(II)[100, 124f] complexes proved to be significantly more powerful (entries 3 and 5), delivering the desired products in synthetically meaningful yields. We then focused on the inexpensive ruthenium(II) complexes and screened various solvents and additives systematically. We found that the chemoselectivity towards the NH-free pyrrole **128a** was strongly influenced by the silver(I) additive and the solvents (entries 5-10).[124f] Finally, the optimal conditions are determined as shown in entry 10. In the presence of $AgSbF_6$ additive, the desired NH-free pyrrole **128a** was obtained in almost quantitative yield in a mixture of DCE and MeOH in the ratio of 2:1.

Table 4. Optimization of transition metal-catalyzed C–H/N–H activation on enamide **127**.[a]

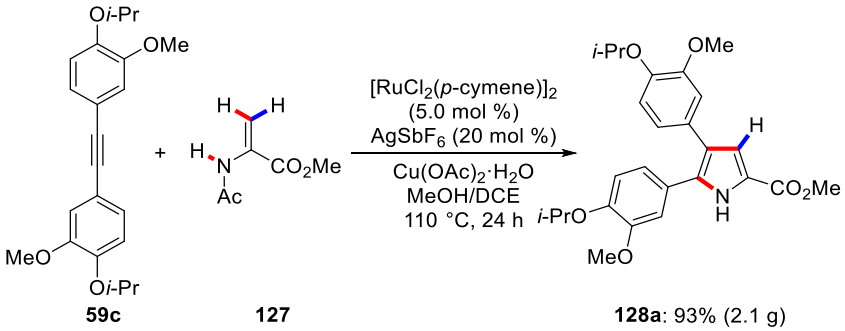


Entry	[TM]	solvent	**128a** (%) R = H	**128a´** (%) R = Ac
1	---	MeOH/DCE	---	---
2	$Cp^*Co(CO)I_2$	MeOH/DCE	---	---
3	$[Cp^*RhCl_2]_2$	MeOH/DCE	94	trace
4	$Pd(OAc)_2$	MeOH/DCE	15	---
5	$[RuCl_2(p\text{-cymene})]_2$	PEG-400[b]	32	59
6	$[RuCl_2(p\text{-cymene})]_2$	PEG-400/H_2O[b]	44	34
7	$[RuCl_2(p\text{-cymene})]_2$	*t*-AmOH[b]	13	80
8	$[RuCl_2(p\text{-cymene})]_2$	*t*-AmOH	68	23
9	$[RuCl_2(p\text{-cymene})]_2$	*t*-AmOH/DCE	95	trace
10	**$[RuCl_2(p\text{-cymene})]_2$**	**MeOH/DCE**	**97**	**---**

[a] Reaction conditions: **59c** (0.50 mmol), **127** (0.55 mmol), [TM] (10 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (2.0-3.0 equiv), solvent (1.5 mL), 110-120 °C, 24 h, yield of isolated products; [b] in the absence of $AgSbF_6$.

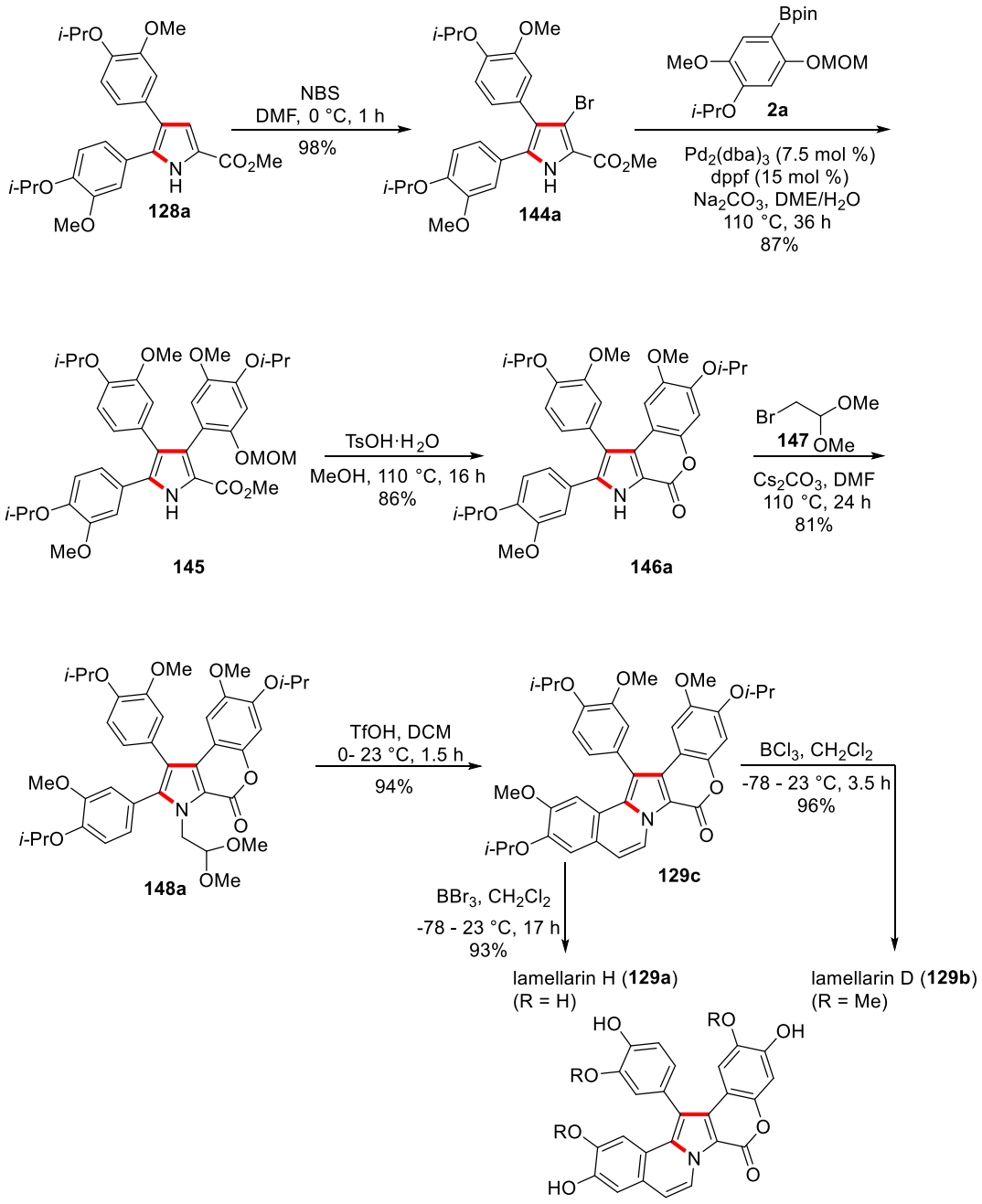
3.3.3 Synthesis of Lamellarin D/H

With the optimized conditions being identified, we then explored the scalability of the C–H/N–H activation with a gram-scale reaction. To our delight, the large scale reaction delivered the desired key intermediate pyrrole **128a** in comparably high yield (Scheme 64).



Scheme 64. Gram-scale synthesis by C–H/N–H activation.

Subsequently, reaction of key intermediate pyrrole **128a** with NBS gave the expected C3-brominated pyrrole **144a** selectively in excellent yield by a judicious choice of solvent.[122e] Next, the Suzuki-Miyaura cross-coupling of **144a** with arylboronic ester **2a** afforded the tetra-substituted pyrrole **145**. With a regioselective route to 3,4,5-arylated pyrrole-2-carboxylates **145** established, we focused on their conversion to the lamellarin scaffold. Thus, compound **145** was treated with *p*-TsOH in methanol to give lactone **146a**, which was alkylated with commercially available bromoacetaldehyde dimethyl acetal **147** using Cs_2CO_3 as base to afford **148a** in 81% yield. Finally, The *N*-alkylated intermediate **148a** was transformed into isoquinoline **129c** in a TfOH-mediated Pomeranz-Fritsch cyclization in 94% yield. The selective deprotection of the isopropyl groups in **148a** with BCl_3 afforded lamellarin D **129b** in 96% yield. Meanwhile, lamellarin H **129a** could be obtained by the cleavage of both methyl and isopropyl groups simultaneously with BBr_3 (Scheme 65).[122f]

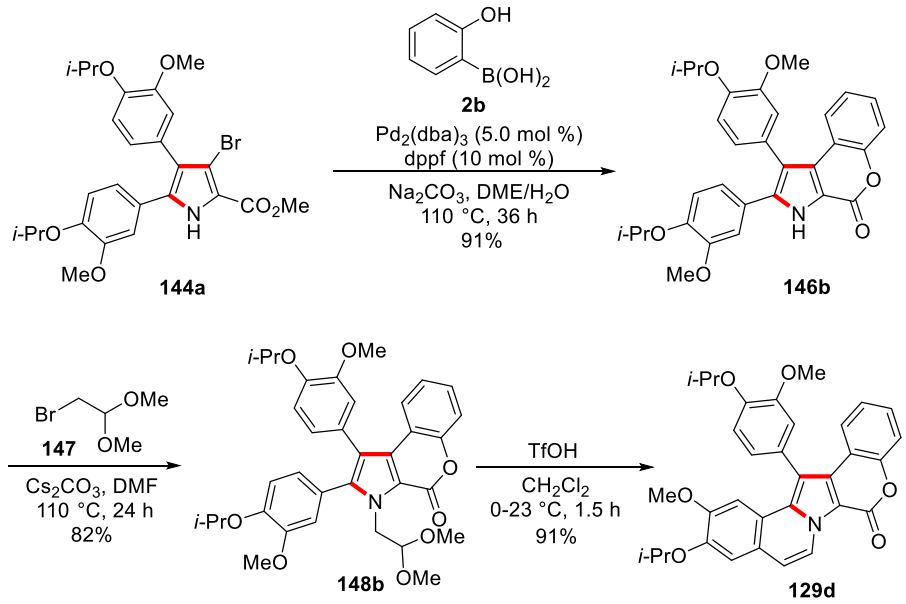


Scheme 65. Synthesis of lamellarins H (**129a**) and D (**129b**).

3.3.4 Synthesis of Lamellarin Derivatives 129d and 129e

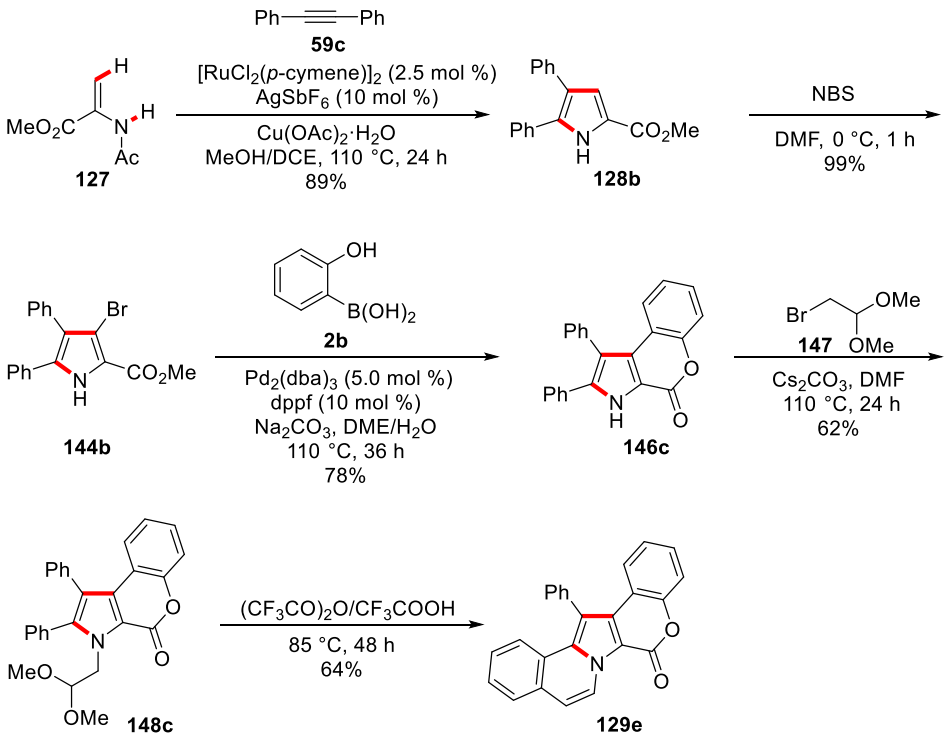
With the concise synthetic route to lamellarins H and D being established, we subsequently prepared the novel lamellarin derivative **129d** being devoid of oxygenation elements at one *β*-aryl motif in only three steps from the the C3-brominated pyrrole **144a** (Scheme 66). To our delight, by utilizing the *ortho* hydroxyl phenyl boronic acid **2b,** we could access the annulated lactone **146** in one step by combining the Suzuki-Miyaura

coupling and intramolecular lactonizaiton. Finally, lamellarin derivative **129d** was again obtained by Pomeranz-Fritsch cyclization.



Scheme 66. Synthesis of lamellarin analogue **129d**.

The strategy of combining the ruthenium(II)-catalyzed C–H/N–H activation with the palladium-catalyzed one-pot annulation further set the stage for the preparation of truncated lamellarin analogue **129e** (Scheme 67), highlighting the modular nature of our approach.



Scheme 67. Synthesis of lamellarin analogue **129e**.

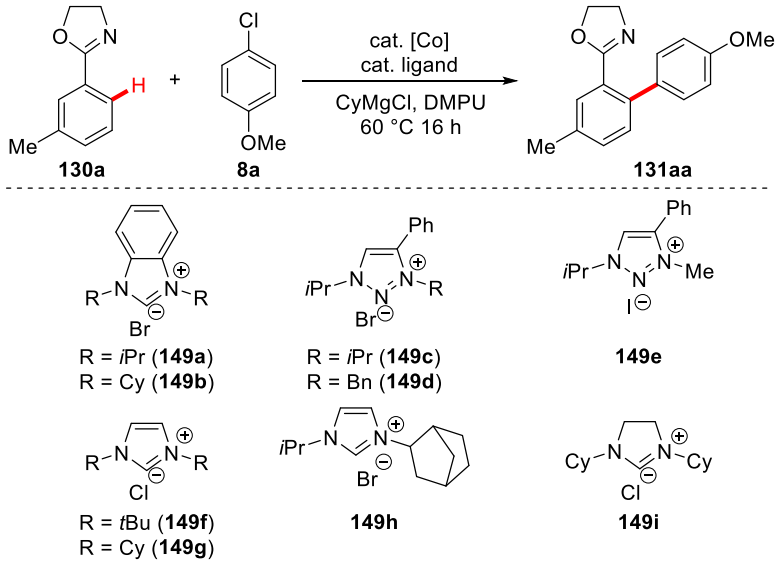
3.4 Cobalt-Catalyzed C–H Functionalizations by Imidate Assistance with Aryl and Alkyl Chlorides

The vast majority of direct C–H arylations has been realized with catalysts of precious 4d transition metals, most notably with the assistance of palladium, rhodium and ruthenium complexes.[96] In consideration of the natural abundance and low costs of 3d transition metals, the focus in C–H activation catalysis has shifted in the recent years towards the use of base metal catalysis. In this context, Ackermann[2k, 61d, 67, 125] and Yoshikai[53e, 66, 68] have recently reported on C–H arylations with organic halides by low-valent cobalt catalysis. Oxazolines are valuable intermediates[105] in organic synthesis as well as useful ligands[126] in metal catalysis. Therefore, within this thesis studies were performed to develop low valent cobalt-catalyzed C–H arylations by oxazoline assistance.

3.4.1 Optimization Studies

We initiated our studies by testing various cobalt salts and ligands for the envisioned C–H arylation on aryl oxazoline **130a** with aryl chloride **8a** (Table 5). Among a variety of *N*-heterocyclic carbene (NHC) preligands derived from benzimidazolium salts **149a–b**, triazolium salts **149c–e**, and imidazolium salts **149f–h** (entries 1–12), dicyclohexyl-substituted imidazolium chloride **149g** gave the best result (entry 8). Imidazolinium salt **149i** also showed good reactivity, with however a slightly decreased yield of the desired product **131aa** (entry 10). Interestingly, the typical NHC precursors IMes·HCl and IPr·HCl failed to deliver the desired product **131aa** in good yields (entries 11 and 12). Among a variety of cobalt salts, $Co(acac)_2$ proved to be optimal (entries 14–17). Importantly, no product was formed in the absence of any cobalt salt (entries 13). Furthermore, the best metal to ligand ratio was determined to be 1/1 (entries 8 and 18). Surprisingly, the reaction proceeded smoothly even at ambient temperature and delivered the desired product in comparable yield (entry 19).

Table 5. Optimization of cobalt-catalyzed C–H arylation by oxazoline assistance.[a]

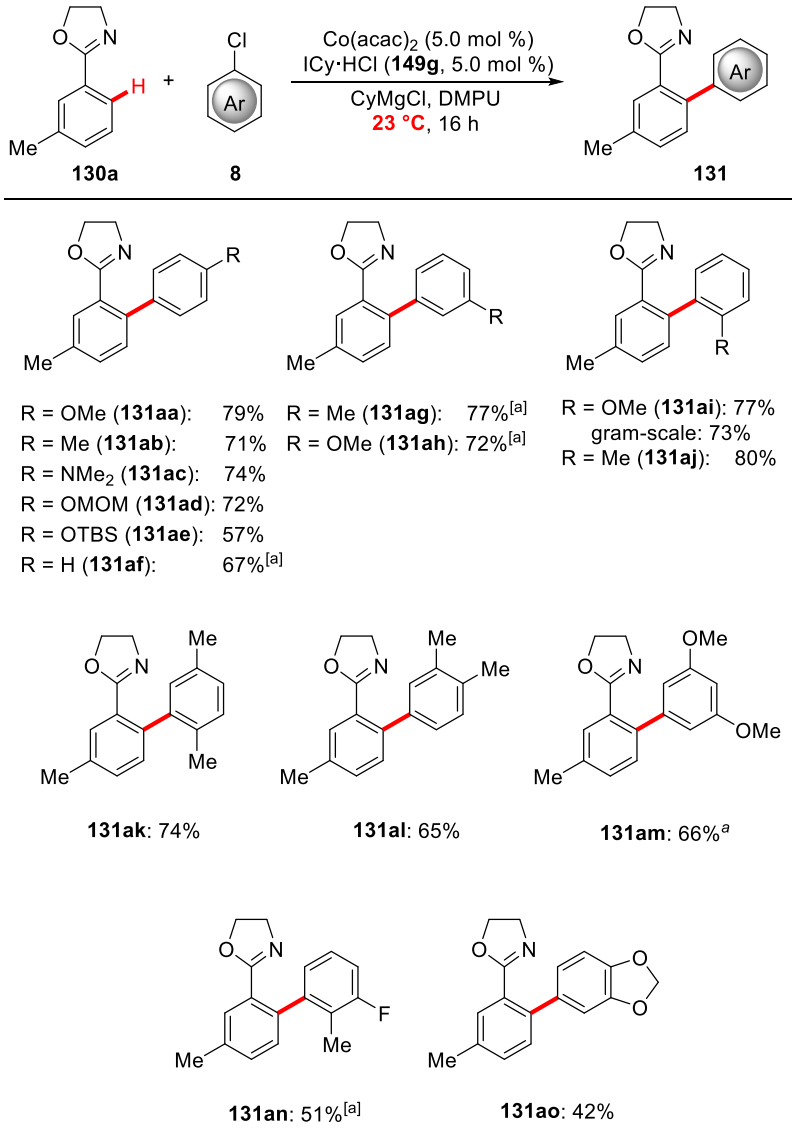


entry	[Co] (mol %)	ligand (mol %)	**131aa** (%)[b]
1	$Co(acac)_2$ (5.0)	---	< 5
2	$Co(acac)_2$ (5.0)	**149a** (5.0)	19
3	$Co(acac)_2$ (5.0)	**149b** (5.0)	27
4	$Co(acac)_2$ (5.0)	**149c** (5.0)	34
5	$Co(acac)_2$ (5.0)	**149d** (5.0)	9
6	$Co(acac)_2$ (5.0)	**149e** (5.0)	20
7	$Co(acac)_2$ (5.0)	**149f** (5.0)	13
8	$Co(acac)_2$ (5.0)	**149g** (5.0)	81
9	$Co(acac)_2$ (5.0)	**149h** (5.0)	14
10	**$Co(acac)_2$ (5.0)**	**149i (5.0)**	**65**
11	$Co(acac)_2$ (5.0)	IMes·HCl (5.0)	13
12	$Co(acac)_2$ (5.0)	IPr·HCl (5.0)	4
13	---	**149g** (5.0)	---
14	$CoCl_2$ (5.0)	**149g** (5.0)	74
15	$CoBr_2$ (5.0)	**149g** (5.0)	67
16	CoI_2 (5.0)	**149g** (5.0)	73
17	$Co(acac)_3$ (5.0)	**149g** (5.0)	51
18	$Co(acac)_2$ (5.0)	**149g** (10.0)	56
19	**$Co(acac)_2$ (5.0)**	**149g (5.0)**	**79**[c]

[a] Reaction conditions: **130a** (0.50 mmol), **8a** (0.65 mmol), CyMgCl (2.0 equiv), DMPU (1.0 mL), 60 °C, 16 h. [b] Yield of isolated product. [c] The reaction was performed at 23 °C.

3.4.2 Scope of Cobalt-Catalyzed C−H Arylation with Aryl Chlorides

Once obtained the best conditions, we then explored the versatility of the optimized catalytic system (Scheme 68). Notably, various aryl chlorides **8** with *para*-, *meta*- and even sterically hindered *ortho*-substituents could be efficiently converted. Functional groups such as, ether, halide or tertiary amine, were well tolerated (**131ac**-**131ae**, **131ao**). The utility of this method was further demonstrated by the 5 mmol-scale reaction, which provided the corresponding product **131ai** in 73% yield.

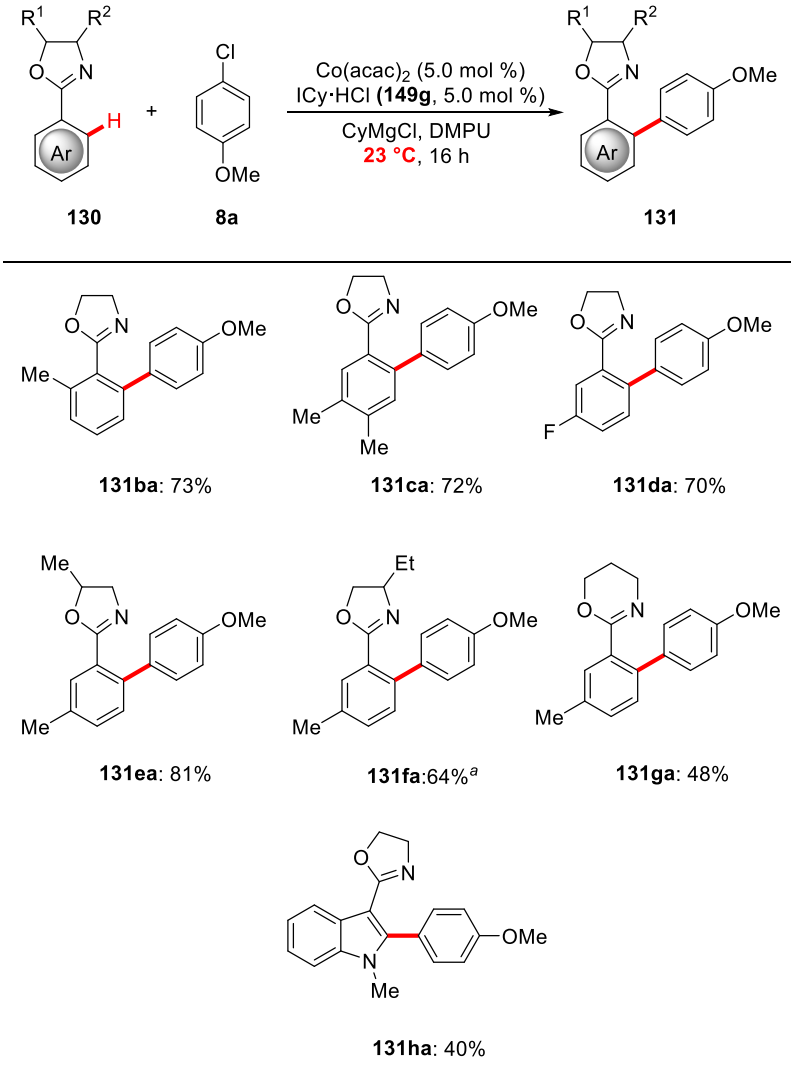


[a] **149i** (5.0 mol %) was used as the ligand.

Scheme 68. Scope of cobalt-catalyzed C−H arylation with respect to aryl chlorides **2**.

Subsequently, a variety of cyclic imidates **130** were tested in the ambient-temperature cobalt-catalyzed C–H arylation (Scheme 69). The protocol was applicable to both electron-rich as well as electron-deficient arenes

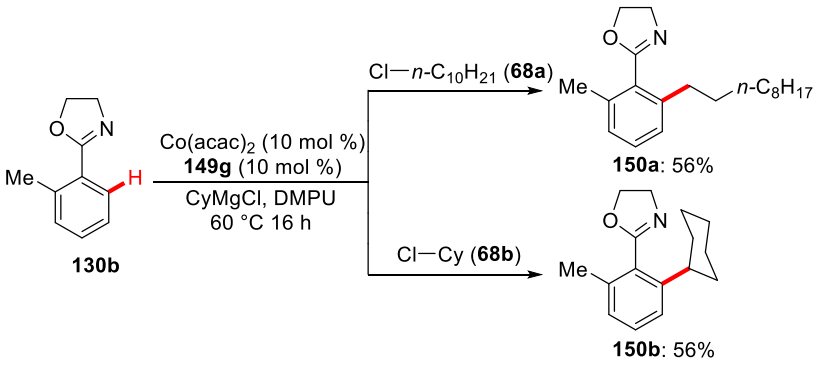
130, thereby delivering the corresponding products **131** with excellent levels of positional selectivity. Furthermore, substituted cyclic imidates **130e-g** with varying ring size were also well tolerated. Heteroaromatic indole substrate **130h** also proved to be a viable substrate for this transformation.



[a] **149i** (5.0 mol %) was used as the ligand

Scheme 69. Cobalt-catalyzed C−H arylation of aryl imidates **130**.

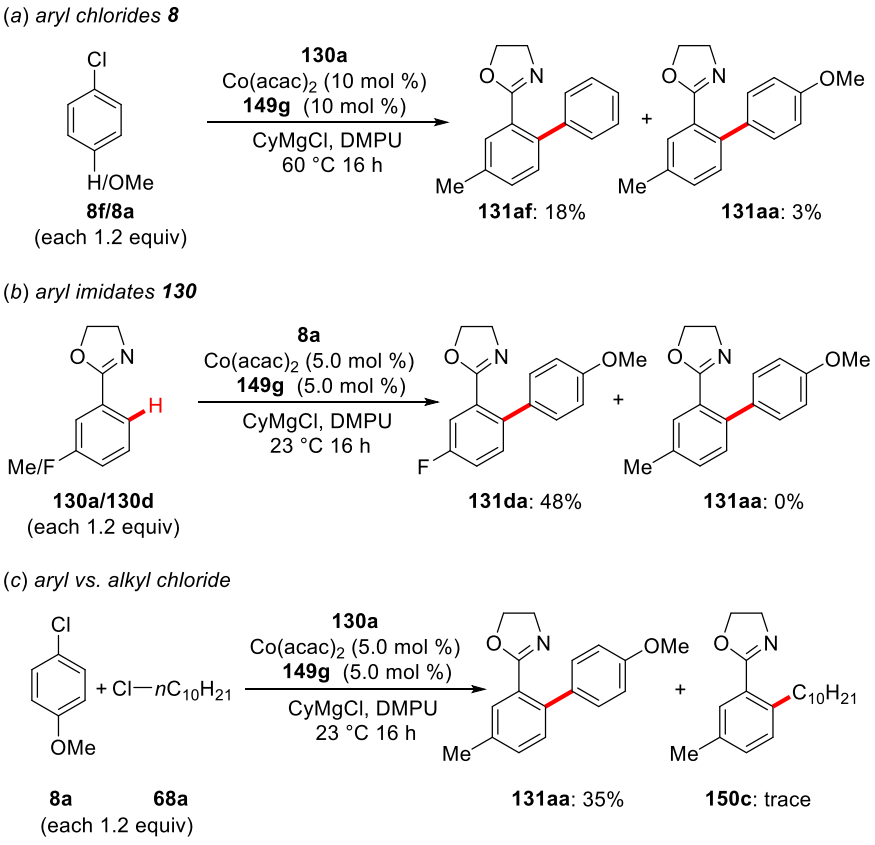
Actually, not only C–H arylations were achieved with this broadly applicable low-valent cobalt-NHC catalyst, but also challenging primary and secondary C–H alkylations were shown to be possible, albeit with moderate yields (Scheme 70).



Scheme 70. Primary and secondary C–H alkylations.

3.4.3. Mechanistic Studies

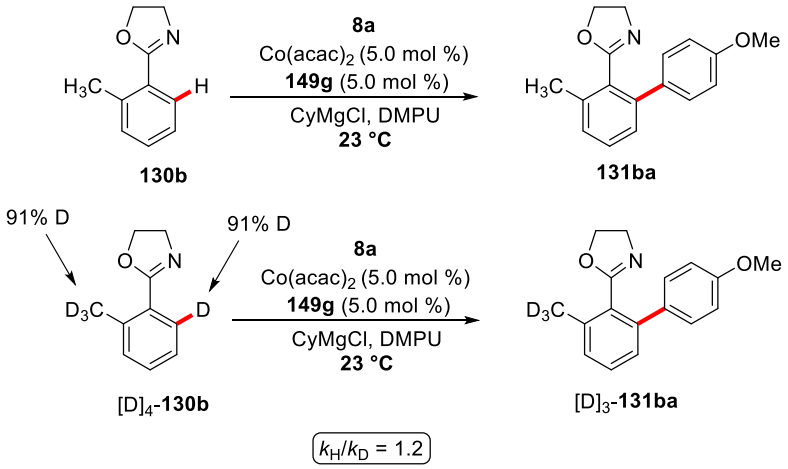
To delineating the working mode of the transformation, we performed a series of competition experiments (Scheme 71). Thus, electron-deficient aryl chloride **8f** was preferentially converted, indicating a kinetically relevant C–Cl cleavage step (Scheme 71a). The intermolecular competition experiment with aryl imidates **130** showed that electron-deficient substrate **130d** reacted exclusively (Scheme 71b).



Scheme 71. Intermolecular competition experiments.

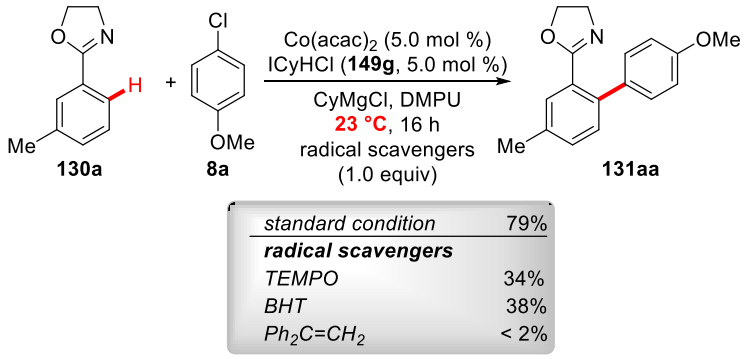
Furthermore, in the competition experiment between arylating and alkylating reagents **8a** and **68a**, we observed the C–H arylated product **131aa** as the main product, while only traces of the alkylated arene **150a** was detected. This result demonstrated the challenging nature of the C–H alkylations.

Furthermore, independent experiments with substrates **130b** and [D]$_4$-**130b** revealed a kinetic isotope effect (KIE) of $k_H/k_D \approx 1.2$, indicating that C–H activation might not be the rate determining step (Scheme 72).



Scheme 72. Kinetic isotope effect study.

We introduced stoichiometric amounts of typical radical scavengers into the catalytic system, and observed that the yield dropped significantly. These results indicated that a single electron transfer (SET)-type process might be operative (Scheme 73).

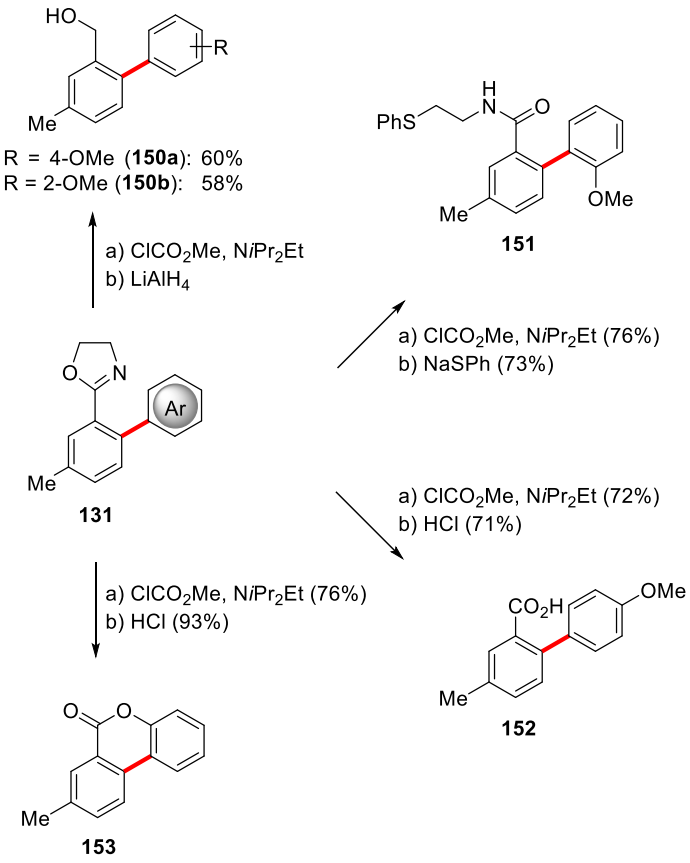


Scheme 73. Cobalt-catalyzed C−H arylation in the presence of radical scavengers.

3.4.4. Diversification of Biaryl Imidates 131

Finally, the synthetic utility of our strategy was further demonstrated by the facile diversification[105b] of the obtained biaryl oxozolines **131**, delivering the alcohols **150**, amide **151**, arylated benzoic acid **152** and

benzochromen-6-one **153** (Scheme 74).[105d] Thereby, a variety of key structural motifs of bioactive compounds were easily accessible by this modifiable directing group strategy.[97, 127]



Scheme 74. Diversification of biaryl imidates **131**.

3.5 Oxazolinyl-Assisted C−H Amidation by Cobalt(III) Catalysis

Decorated oxazolines are important structural motifs of various bioactive compounds of relevance to crop protection and medicinal chemistry (Figure 4).[106] Moreover, oxazolines are easily accessible and can be transformed into a variety of valuable functional groups,[128] which renders them key intermediates in organic synthesis and useful ligands in metal catalysis.[126] Consequently, the development of flexible methods that provide general access to substituted oxazolines are highly desirable.

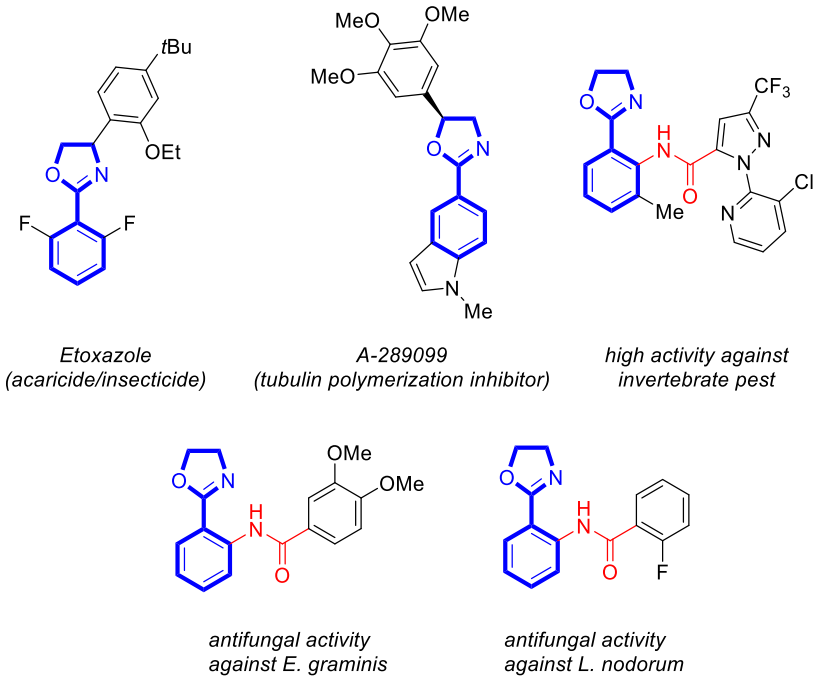


Figure 4. Selected bioactive 2-aryl oxazolines.

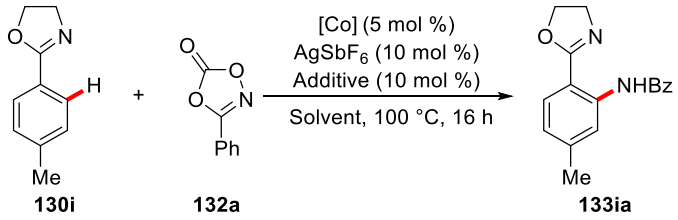
In recent years, transition metal-catalyzed C−H functionalization has made important progress for the atom- and step-economic diversification of oxazolines.[20e, 25] However, catalytic C−H amidations on aryl oxazolines are as of yet restricted to the use of precious rhodium and iridium catalysts, as developed by Chang, among others.[107] As a result, in this chapter we started to explore the possibility for cobalt(III)-catalyzed C−H amidations of oxazolines by employing dioxazolones[129] as user-friendly amidating reagent.

3.5.1 Optimization Studies

At the outset of our studies, we explored the feasibility of the envisioned cobalt-catalyzed C−H amidation of aryl oxazoline **130i** with dioxazolone **132a** (Table 6). Preliminary solvent optimization showed that aprotic solvents enabled the desired C−H amidation, with DCE being optimal (entries 1−3). Then a variety of additives, including mono protected Amino acid (MPAA), were tested. NaOAc proved to be the most effective (entries 3−10). These observations demonstrated the importance of carboxylate assistance in the

C−H functionalization regime (entries 3−10). Different cobalt(III) complexes were explored thereafter. While $CpCo(CO)I_2$ and $CoCl_2$ proved to be completely unreactive, $[Cp^*CoI_2]_2$ and $[Cp^*Co(MeCN)_3](SbF_6)_2$ showed similar reactivity with $Cp^*Co(CO)I_2$, albeit with inferior yields (entries 10−14). A control experiment revealed that there was no reaction in the absence of cobalt catalyst (entry 16). The beneficial effect of the carboxylate additive was further verified by the result of entry 15.

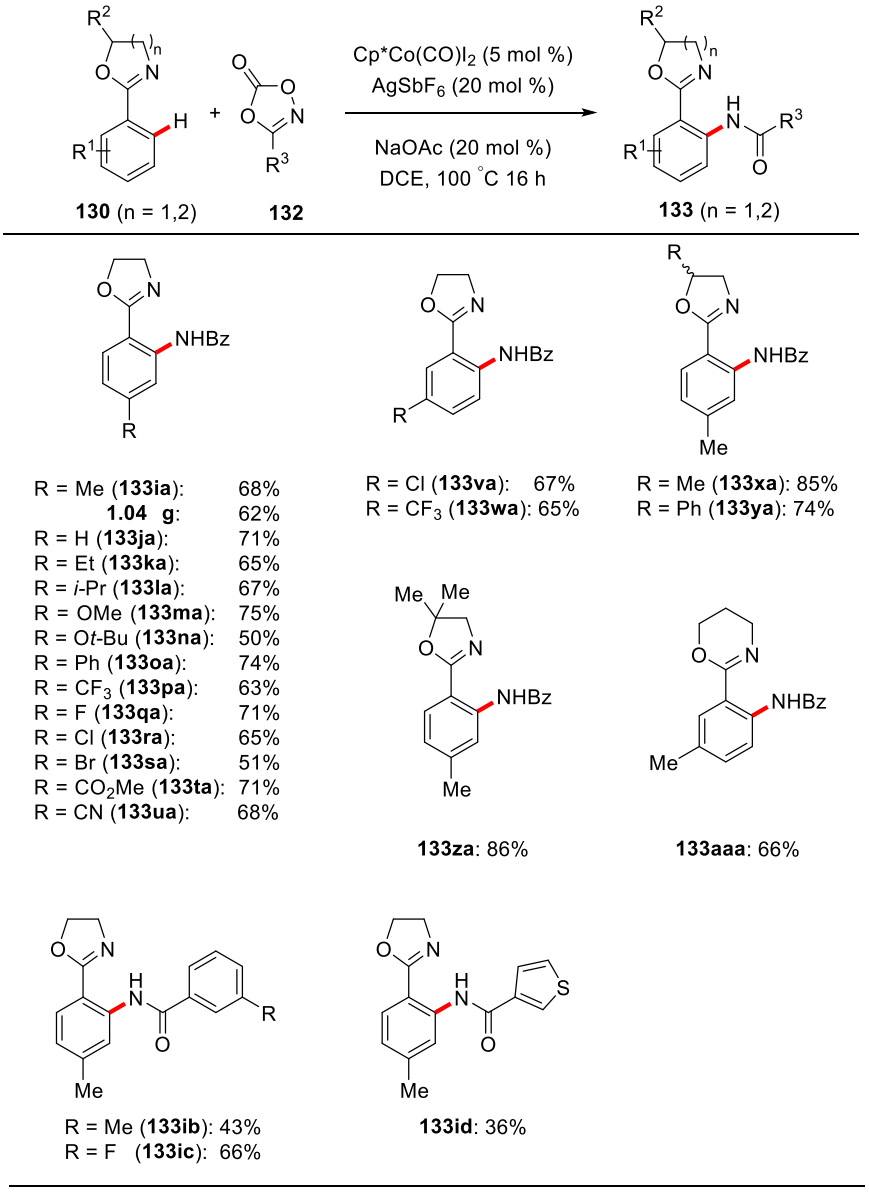
Table 6. Oxazolinyl-assisted C−H amidation.[a]



Entry	[Co]	Solvent	Additive	**133ia**
1	$Cp^*Co(CO)I_2$	TFE	NaOAc	–
2	$Cp^*Co(CO)I_2$	$PhCF_3$	NaOAc	53
3	$Cp^*Co(CO)I_2$	DCE	NaOAc	65
4	$Cp^*Co(CO)I_2$	DCE	KOAc	47
5	$Cp^*Co(CO)I_2$	DCE	PivOH	58
6	$Cp^*Co(CO)I_2$	DCE	PivONa	63
7	$Cp^*Co(CO)I_2$	DCE	$MesCO_2Na$	3
8	$Cp^*Co(CO)I_2$	DCE	$AdCO_2Na$	44
9	$Cp^*Co(CO)I_2$	DCE	Ac-Ile-CO_2Na	17
10	**$Cp^*Co(CO)I_2$**	**DCE**	**NaOAc**	**68**[b]
11	$[Cp^*CoI_2]_2$	DCE	NaOAc	61[b]
12	$CpCo(CO)I_2$	DCE	NaOAc	–
13	$CoCl_2$	DCE	NaOAc	–
14	$[Cp^*Co(MeCN)_3](SbF_6)_2$	DCE	–	54
15	$Cp^*Co(CO)I_2$	DCE	–	35
16	–	DCE	NaOAc	–

[a] Reaction conditions: **130i** (0.50 mmol), **132a** (1.2 equiv), [Co] (5.0 mol %), $AgSbF_6$ (10 mol %), additive (10 mol %) solvent (2.0 mL), 100 °C, 16 h. [b] $AgSbF_6$ (20 mol %), NaOAc (20 mol %).

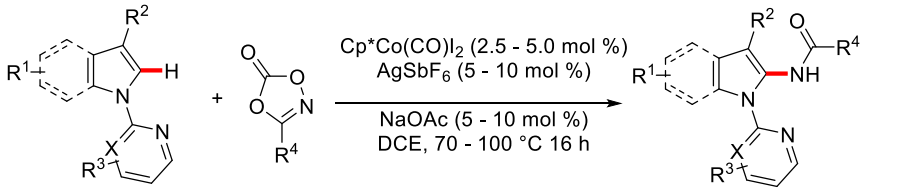
3.5.2 Scope of the Oxazolinyl-Assisted C−H Amidation



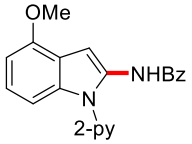
Scheme 75. Scope of the oxazolinyl-assisted C−H amidation.

With the optimized conditions identified, we tested the cobalt(III) catalyst in the C−H amidation of various aryl oxazolines **130** (Scheme 75). Thus, a remarkable functional group tolerance that included chloro-, bromo-, cyano-, ester- and trifluromethyl-substituents was observed, which highlighted the excellent chemo-selectivity of this cobalt(III) catalysis (**130m-v**). For the *meta*-substituted arenes **130v-w** featuring two inequivalent *ortho* C−H bonds an excellent positional selectivity was observed, which was fully controlled by oxazolinyl assistance and secondary steric interactions. Thereafter, we tested substrates bearing substituents on the oxazoline ring. Thus, oxazolines **130** derived from different *β*-amino alcohols gave the desired products

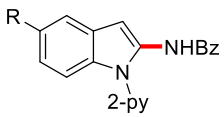
133xa−**133za** with synthetically meaningful yields. Interestingly, the six-membered ring 1,3-oxazine **130aa** also smoothly delivered the corresponding product. The efficiency of the protocol was further demonstrated by the gram-scale synthesis of amide **133ia** in comparable yield.



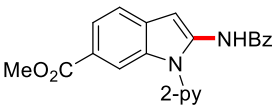
102 **132** **154** (X = CH, N)



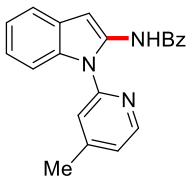
154aa: 96%



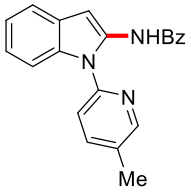
R = H (**154ba**): 94%
1.84 g: 98%
R = OMe (**154ca**): 98%
R = F (**154da**): 93%
R = Br (**154ea**): 95%
R = I (**154fa**): 82%



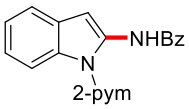
154ga: 91%



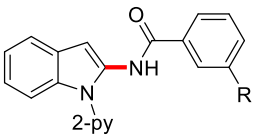
154ha: 97%



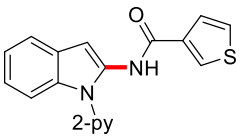
154ia: 92%



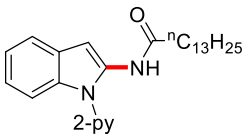
154ja: 94%



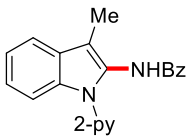
R = Me (**154bb**): 98%
R = F (**154bc**): 76%
R = Cl (**154be**): 65%



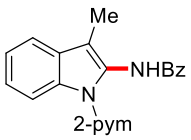
154bd: 96%



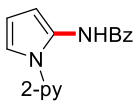
154bf: 98%



154ka: 64 %



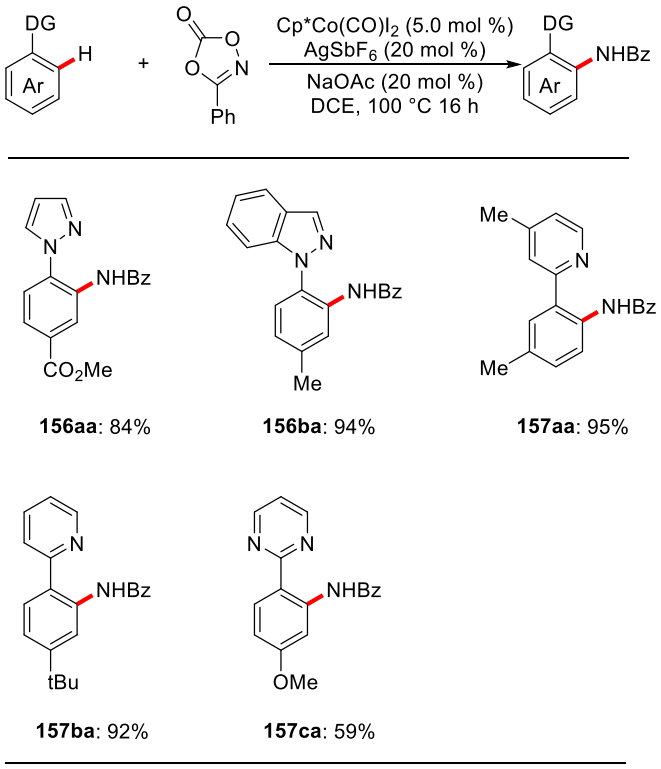
154la: 65%



155aa: 55%

Scheme 76. Cobalt(III)-catalyzed C−H amidation of indoles and pyrroles.

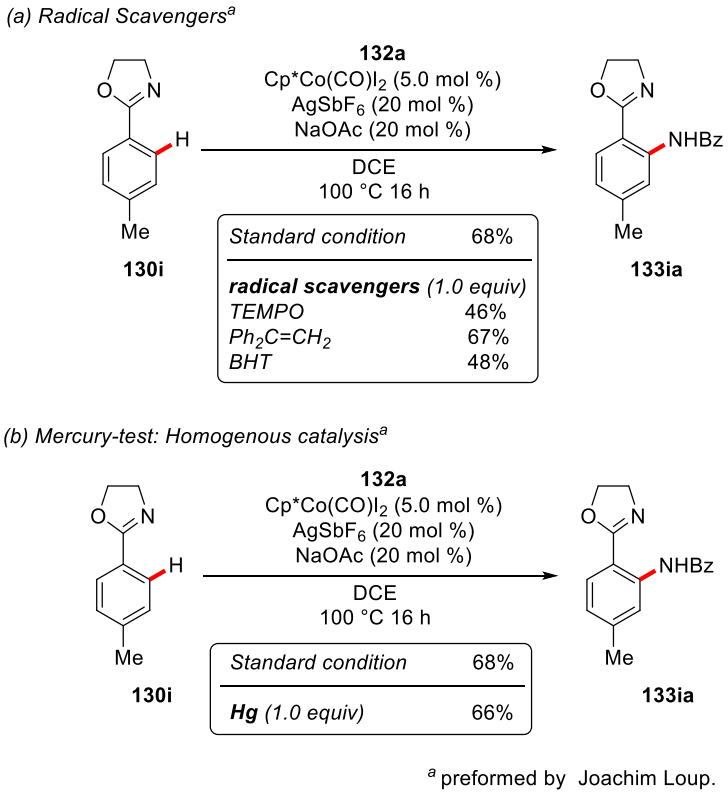
To our delight, apart from oxazolines and oxazines **130,** indoles **102** bearing removable pyridyl and pyrimidyl directing group also proved to be viable substrates for the Cp*Co(CO)I_2-catalyzed C−H amidation (Scheme 76). Again, the excellent chemoselectivity of the cobalt(III) catalyst was demostrated by a remarkable tolerance of valuable electrophilic functional groups, such as fluoro, chloro, bromo, iodo, ester or thiophene substituents (**154ca**−**154ga**). Meanwhile, aryl, heteroaryl, and alkyl amide moieties could be introduced in a step-economical manner by this user-friendly protocol (**154bb**−**154bf**). The robustness of the Cp*Co(CO)I_2-catalyzed C−H amidation was illustrated by the gram-scale synthesis of amidated indole **154ba** at low catalyst loading of only 1.0 mol %. The catalytic system was not only applicable to indole substrates but also enabled the cobalt-catalyzed C−H nitrogenation of pyrroles (**155aa**), pyrozoles (**156aa-156ba**), phenyl pyridines and phenyl pyrimidines (**157aa-157ca**) as well (Scheme 77).



Scheme 77. Cobalt(III)-catalyzed C−H amidation of other substrates.

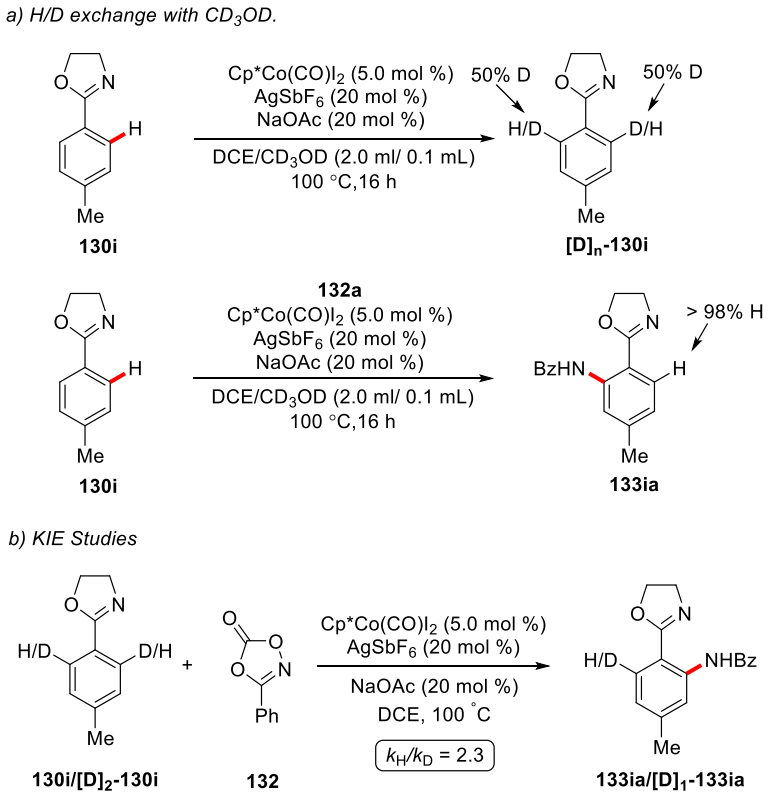
3.5.3 Mechanistic Studies

Attracted by the robustness of the cobalt(III)-catalyzed C−H amidation, we conducted mechanistic studies to elucidate its mode of action. Only a minor loss in catalytic activity was observed when typical radical scavengers were introduced into the catalytic system. These findings do not provide support for a radical-based mechanism (Scheme 78a). Furthermore, a mercury-test experiment confirmed the cobalt catalysis to be homogeneous in nature (Scheme 78b).



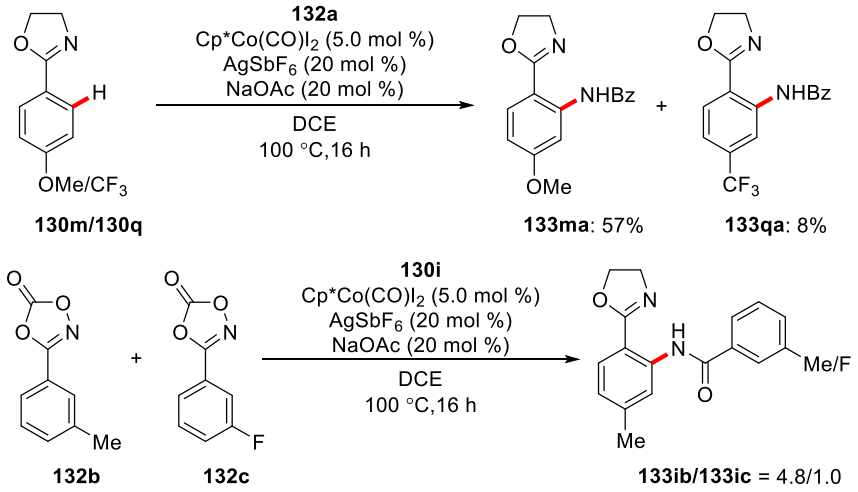
Scheme 78. Radical scavenger experiments and mercury test.

In the absence of the dioxazolinone **132a**, reactions performed in the presence of an isotopically labelled cosolvent revealed a considerable H/D scrambling (Scheme 79a). However, no H/D exchange was observed in the presence of dioxazolinones **132a** (Scheme 79b). The kinetic isotope effect (KIE) was determined to be $k_H/k_D \approx 2.3$ by independent experiments. This result indicated that the C−H cobaltation step might be kinetically relevant.



Scheme 79. H/D exchange and KIE studies.

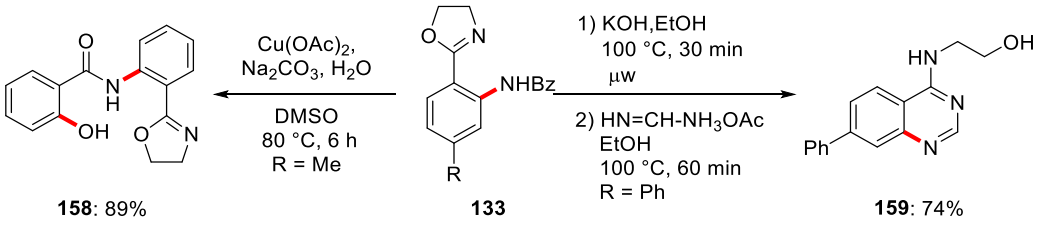
Intermolecular competition experiments between differently substituted substrates revealed electron-rich arenes **130m** and electron-rich dioxazolones **132b** to be converted preferentially (Scheme 80). These results could be rationalized in terms of the key C−H activation step occurring by a base-assisted, intermolecular electrophilic substitution-type (BIES) C−H activation.



Scheme 80. Competition experiments.

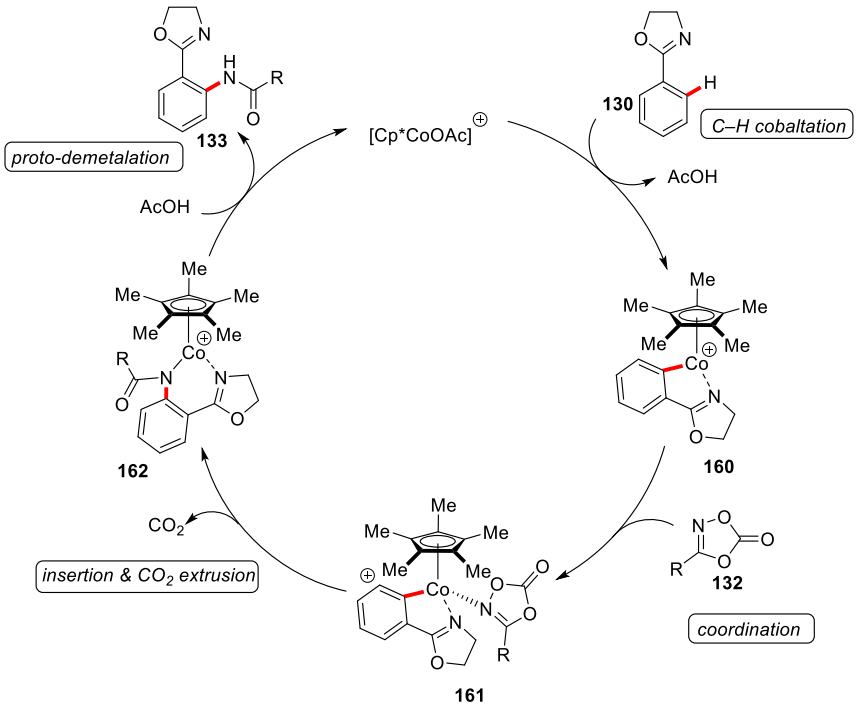
3.5.4 Product Diversivications

The synthetic utility of the cobalt(III)-catalyzed C−H amidation was illustrated by the postsynthetic diversification of the obtained amides **133** (Scheme 81). Thus, the liberation of the free primary amine was easily accomplished within 30 min by microwave irradiation, and then following a modified procedure, a novel quinazolinone **159** could be prepared in a step-economical manner. Moreover, adopting Yu's protocol [130] our catalytic product could easily underwent C−H oxygenation process *via* copper catalysis.



Scheme 81. Diversification of 2-amidoaryloxazolines **133**.

Based on our mechanistic studies and previous reports,[131] we propose a plausible catalytic cycle as follow (Scheme 82): First, a kinetically relevant, acetate-assisted C−H cobaltation occurres to form the metallacycle **160**. Subsequent coordination of the dioxazolones **132** forms the intermediate **161**, which then undergoes CO_2 extrusion. Finally, proto-decobaltation by the originally formed AcOH regenerates the catalyst cobalt-(III) carboxylate and yields the desired product **133.**



Scheme 82. Proposed catalytic cycle.

3.6 Cobalt-Catalyzed Oxidase C−H/N−H Alkyne Annulation

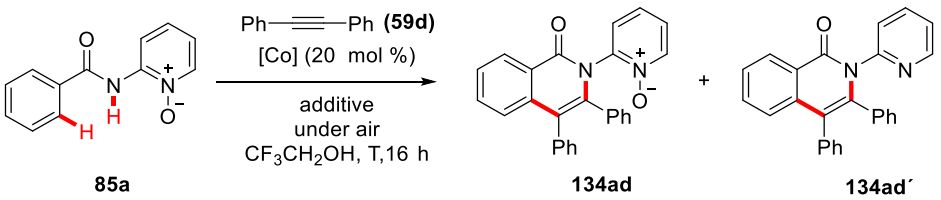
Recent years have witnessed considerable progress in the development of oxidative C−H/Het−H functionalizations for the assembly of bioactive heterocycles,[2l] the vast majority of which require metal oxidants, such as antibacterial copper(II) and/or precious silver(I) oxidants. In contrast, oxidase alkyne annulations with O_2 as the sole oxidant were as of yet only accomplished exploiting precious 4d transition metals such as palladium, rhodium, and ruthenium.[132]

Inspired by recent advances in oxidative cobalt(II)-catalyzed alkene and alkyne annulations by Daugulis,[71-72] Ackermann[108] and Song,[109] we started to explore the possibilities of using oxygen as the sole oxidant in cobalt-catalyzed alkyne annulations.

3.6.1 Optimization Studies

We initiated our studies by testing different additives for the envisioned aerobic cobalt-catalyzed C–H functionalization of arene **85a**, featuring the bidentate 2-pyridyl-*N*-oxide (PyO) as the directing group (Table 7). Thus, the envisioned cobalt oxidase reactivity was realized under an atmosphere of ambient air, when using PivOH as additive in trifluoroethanol (TFE) at 80 °C (entries 1-2). While high reacting temperature was detrimental for the reaction, the most appropriate temperature was determined to be 60 °C (entries 3-4). No products were observed when the reaction was conducted under a N_2 atmosphere (entry 5), this result clearly demonstrated that O_2 is sole oxidant in this transformation. The catalyst loading could be further reduced to 10 mol % when the reaction was performed under an atmosphere of O_2 (entries 6-7). In the absence of either cobalt salt or PivOH, no product was detected (entries 8-9). Finally, after *N*-deoxygenation with PCl_3, the desired product could be isolated in 84% yield (entry 10). Subsequently, different cobalt sources (entries 11-16) and solvents (entries 17-19) were tested, $Co(OAc)_2$ and TFE proved to be optimal. It is worth noting that the cobalt(III) complexes [Cp*Co(CO)I_2], $[Co(NH_3)_6]Cl_3$, and $Co(acac)_3$ failed to deliver the desired product. Furthermore, no reactivity was observed when the PyO directing group was modified to the simple *N*-pyridyl or the *N*-phenyl group. Importantly, this oxidative C–H/N–H functionalization was realized with the simple $Co(OAc)_2$ in combination of O_2, thereby avoiding the expensive Cp* ligand and stoichiometric amounts of silver salt.

Table 7. Optimization of the cobalt-catalyzed oxidase C−H functionalization with internal alkyne **59d**.[a]



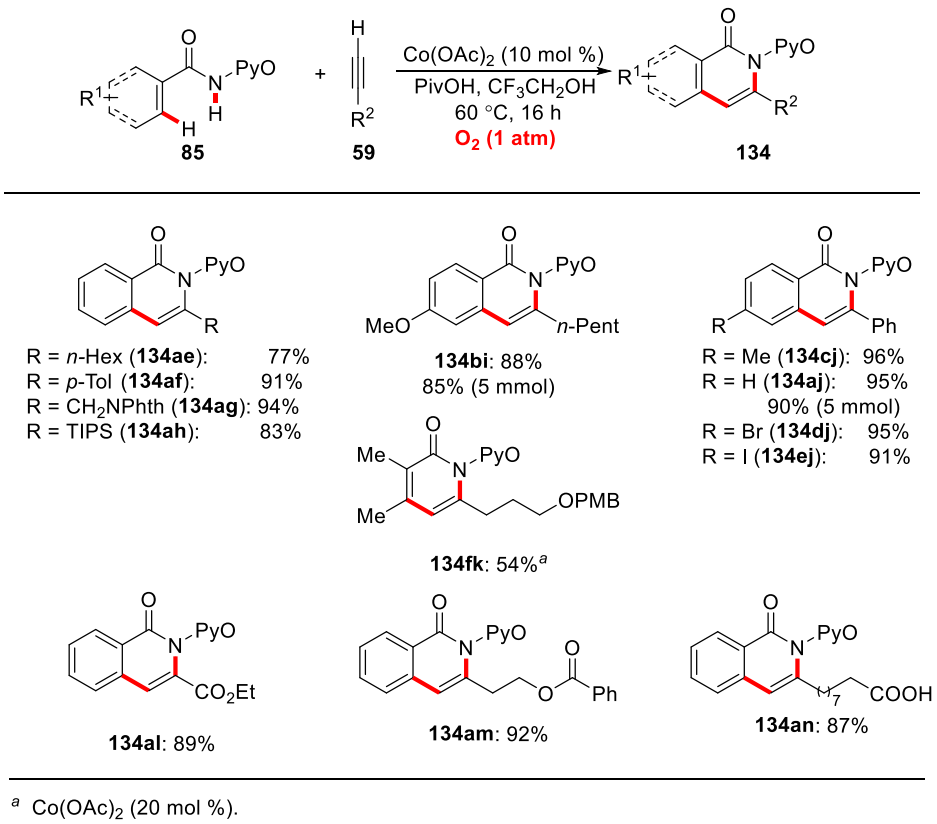
Entry	[Co]	Additive	T (°C)	Yield [%]	
				134ad	**134ad´**
1	$Co(OAc)_2$	NaOPiv	80	---	---
2	$Co(OAc)_2$	PivOH	80	50	25
3	$Co(OAc)_2$	PivOH	100	trace	---
4	$Co(OAc)_2$	PivOH	60	69	26
5[b]	$Co(OAc)_2$	PivOH	60	---	---
6[c]	$Co(OAc)_2$	PivOH	60	28	13
7[c,d]	**$Co(OAc)_2$**	**PivOH**	**60**	**69**	**21**
8	---	PivOH	60	---	---
9	$Co(OAc)_2$	---	60	---	---
10[c, d, e]	**$Co(OAc)_2$**	**PivOH**	**60**	**---**	**84**
11	$CoCl_2$	PivOH	60	---	---
12	CoI_2	PivOH	60	---	---
13	$Co(acac)_2$	PivOH	60	42	10
14[c]	$Co(acac)_3$	PivOH	60	---	---
15[c]	$[Co(NH_3)_6]Cl_3$	PivOH	60	---	---
16[c]	$Cp^*Co(CO)I_2$	PivOH	60	---	---
17[f]	$Co(OAc)_2$	PivOH	60	trace	---
18[g]	$Co(OAc)_2$	PivOH	60	---	---
19[h]	$Co(OAc)_2$	PivOH	60	---	---

[a] Reaction conditions: **85a** (0.25 mmol), **59d** (1.50 equiv), [Co] (20 mol %), additive (2.0 equiv), CF_3CH_2OH (1.0 mL), under air (1 atm), 16 h, isolated yield. [b] under N_2. [c] [Co] (10 mol %). [d] O_2 (1 atm). [e] **59d** (1.2 equiv), isolated after *N*-deoxygenation with PCl_3. [f] $CF_3CH(OH)CF_3$ (1.0 mL) as solvent. [g] EtOH (1.0 mL) as solvent. [h] DMSO (1.0 mL) as solvent.

3.6.2 Scope of Cobalt-Catalyzed Aerobic C−H Functionalization

3.6.2.1 Scope of Terminal Alkynes

With the optimized reaction conditions in hand, we then tested the versatility of the cobalt(II) catalyst with a representative set of benzamides **85a** (Scheme 83) and alkynes. To our delight, a variety of terminal alkynes **59** were efficiently converted in this aerobic C−H/N−H functionalization process. Alkyl-, aryl-, silyl- and ester-substituted terminal alkynes proved to be viable substrates for this transformation. It is worth noting that an excellent tolerance of valuable electrophilic functional groups was observed, such as iodo, bromo, ester, ketone, and carboxylic acid substituents. Interestingly, this strategy was not restricted to aromatic C−H functionalization, but proved applicable to diversification of alkene **85f** as well. The synthetic utility of the optimized cobalt(II) catalyst was further demonstrated by the gram-scale preparation of isoquinolones **134bi** and **134aj** in comparable yields.



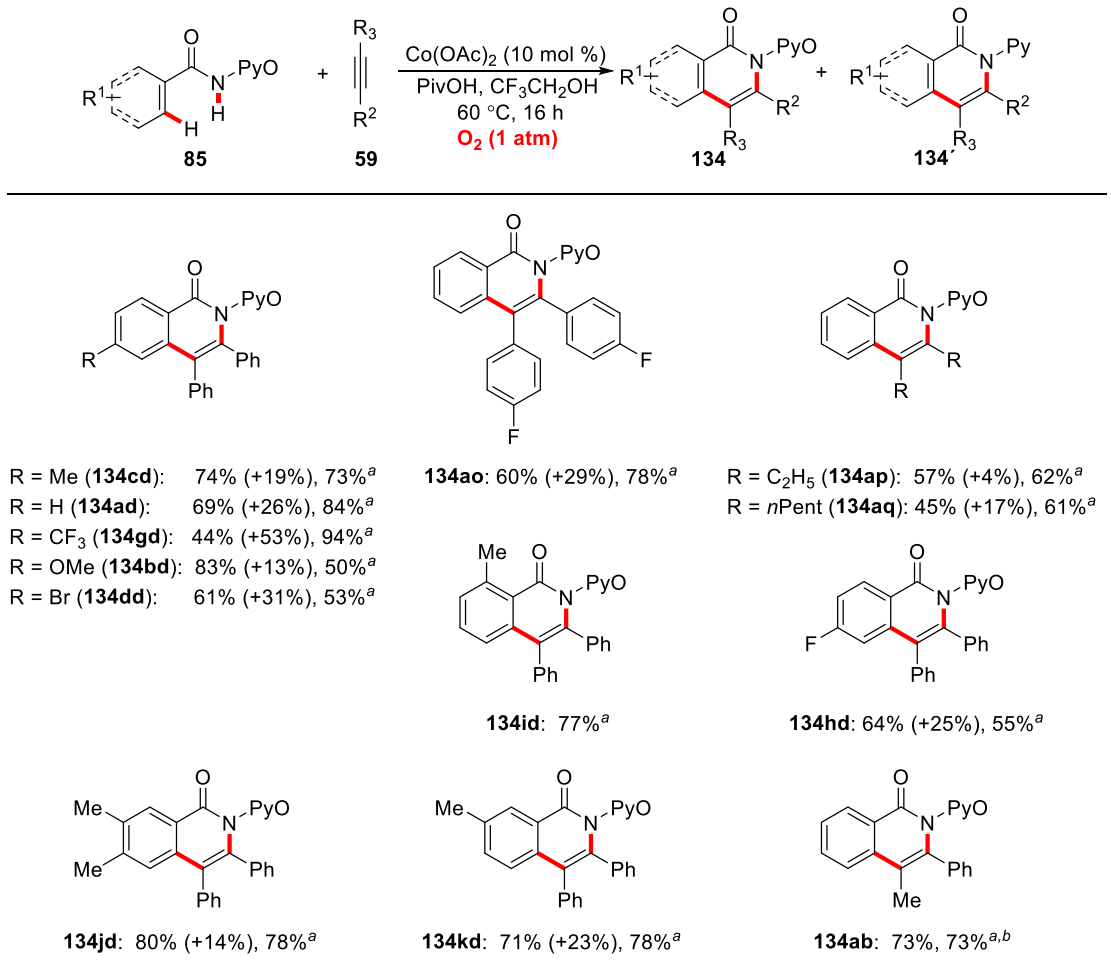
[a] $Co(OAc)_2$ (20 mol %).

Scheme 83. Scope of cobalt-catalyzed aerobic C−H functionalization with terminal alkynes.

3.6.2.2 Aerobic C–H/N–H Functionalizations with Internal Alkynes

The aerobic cobalt-catalyzed C–H/N–H functionalization was not restricted to terminal alkynes **59**. Indeed, challenging internal alkynes **59d**, **59o-q** also proved to be viable substrates for this chemoselective annulation

of benzamides **85** (Scheme 84). Not only symmetrical aryl and alkyl-substituted alkynes were efficiently converted (**59o**-**59q**), but the unsymmetrically internal aryl alkyl-alkyne **59b** also underwent the desired annulation with excellent regio-selectivity, placing the aromatic group proximal to the heteroatom. A variety of valuable substituents in the *para*-, *ortho*- and *meta*-positions of benzamides **85** were well accommodated. For the *meta*-substituted benzamides, the annulation occured preferentially at the least hindered position (**85j**-**85k**).

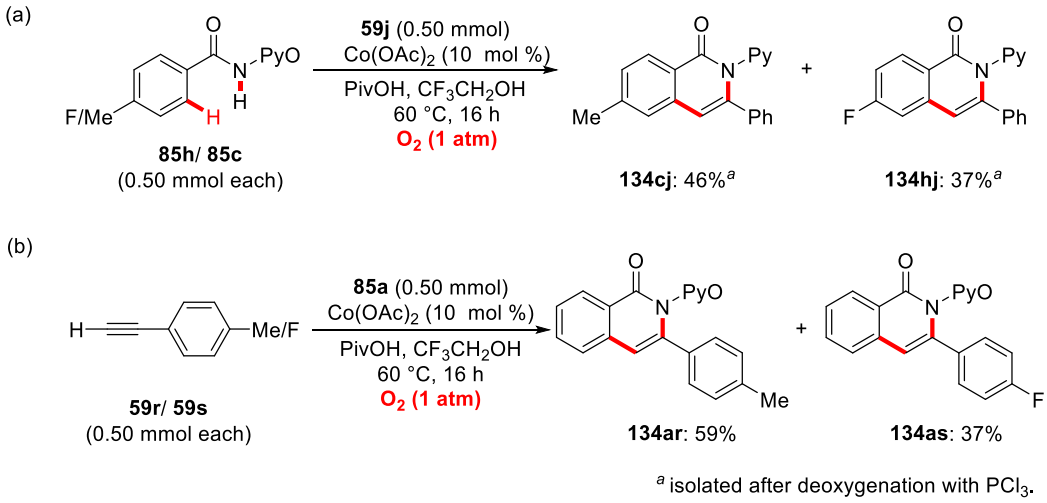


[a] Isolated yields of products **134'** after *N*-deoxygenation with PCl_3. [b] Regioisomeric ratio 16 :1.

Scheme 84. Scope of cobalt oxidase C−H functionalization with internal alkynes.

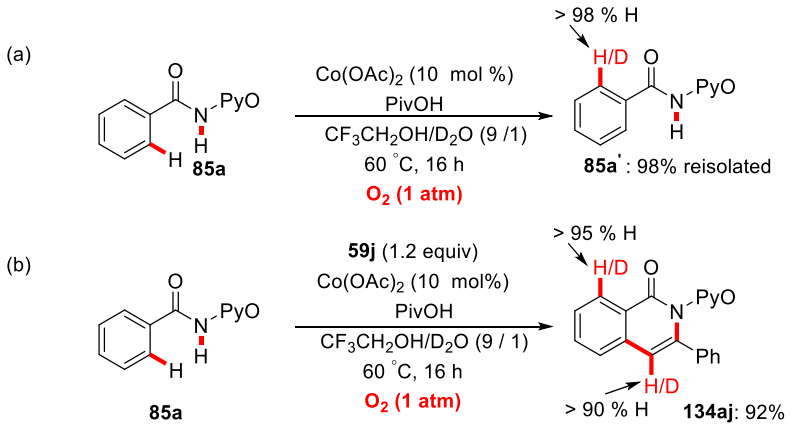
3.6.3 Mechanistic Studies

Thereafter, we performed experimental mechanistic studies to delineate the working mode of the cobalt oxidase catalysis. Intermolecular competition experiments with differently substituted substrates showed that electron-deficient benzamides **85h** and electron-deficient alkynes **59s** are inherently less reactive (Scheme 85).



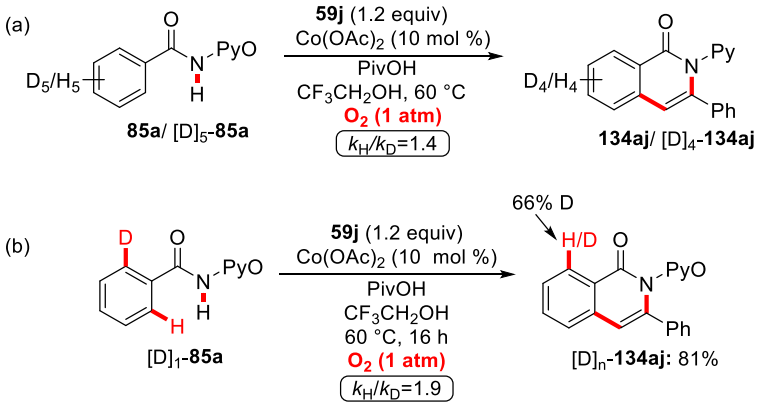
Scheme 85. Intermolecular competition experiments.

Moreover, H/D exchange experiments were performed with D_2O as the co-solvent. No deuterium-incorporation was observed in both the reisolated starting material **85a´** as well as the desired product **134aj**. These results indicated that the C−H cobaltation might be an irreversible process in this transformation (Scheme 86).



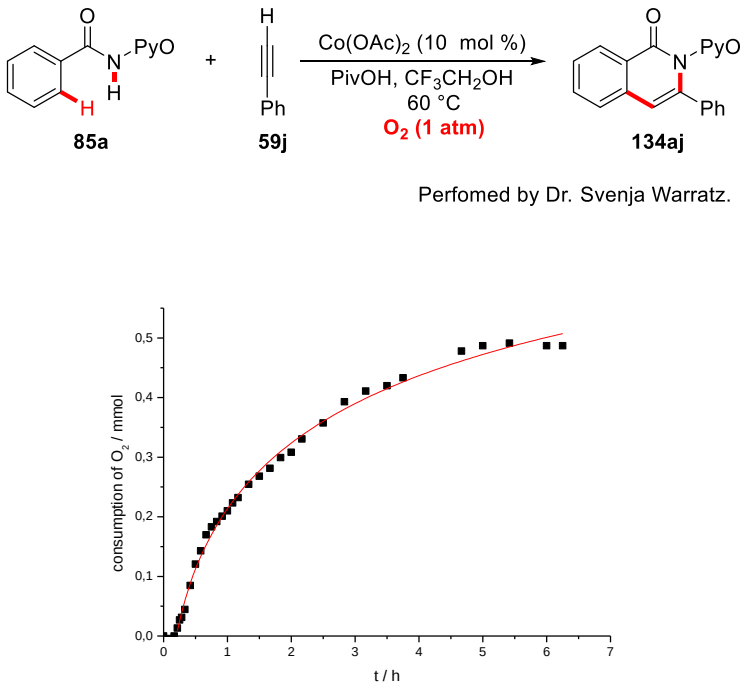
Scheme 86. Attempted H/D Exchange experiments using D_2O as cosolvents.

In addition, inter- and intramolecular kinetic isotope effects (KIE) were determined to be k_H/k_D 1.4 and 1.9, respectively, which were suggestive of a kinetically-relevant C−H cobaltation event (Scheme 87).



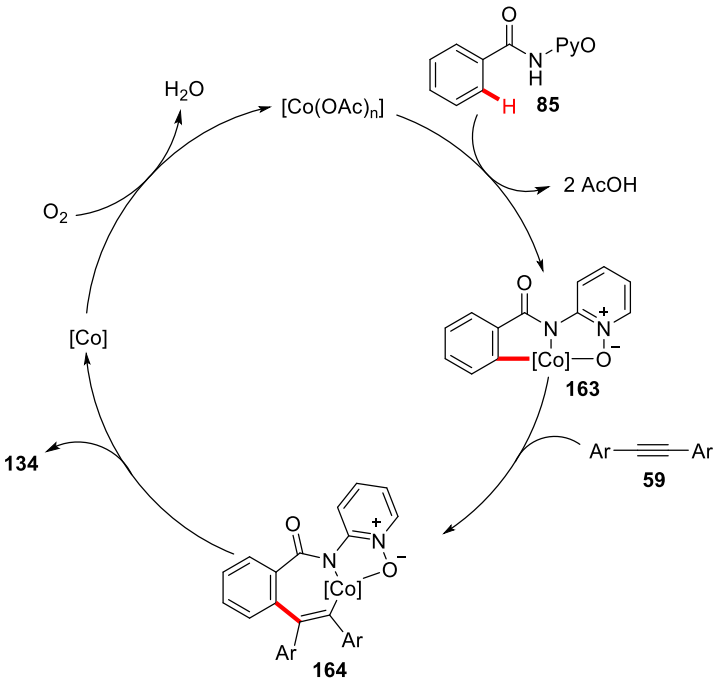
Scheme 87. Kinetic isotope effect (KIE) studies.

For the further understanding of the aerobic nature of this cobalt-catalyzed C−H activation process, O_2 up-take studies were subsequently carried out (Scheme 88). Impressively, the high catalytic efficiency of the cobalt oxidase strategy was demonstrated with 90% conversion of substrate **85a** within less than 5 h. Our observation clearly showed that O_2 served as the sole terminal oxidant in the C−H functionalization process. These results also highlighted a short, yet significant induction period.



Scheme 88. Oxygen consumption during cobalt-catalyzed C−H activation.

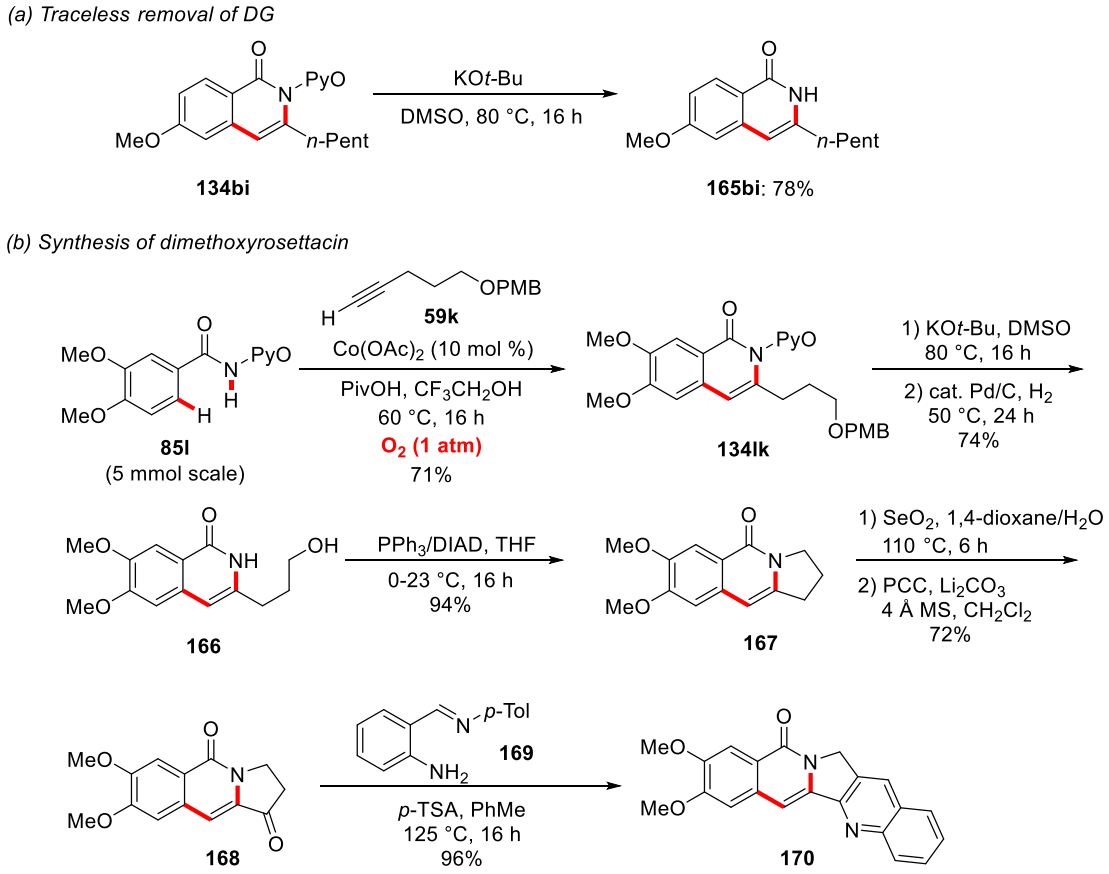
Based on the above mentioned mechanistic studies, a possible catalytic cycle was proposed as follows. The oxidative alkyne annulation is initiated by a kinetically relevant, carboxylate-assisted C−H cobaltation, followed by subsequent migratory insertion of the alkyne **59**, to give the seven membered-caboltacycle **164**. Finally, the reductive elimination delivers the desired isoquinolone product **134** and regenerates the active cobalt species (Scheme 89).



Scheme 89. Plausible catalytic cycle for cobalt catalyzed alkyne anulation.

3.6.4 Product Diversification

Finally, the pyridyl-*N*-oxide moiety was removed in a traceless fashion, which highlighted the considerable synthetic potential of the cobalt-catalyzed oxidase C−H/N−H functionalization (Scheme 90a). Furthermore, we successfully utilized this strategy for the synthesis of the cytotoxic topoisomerase-I (topo-I) inhibitor rosettacin derivative **170** (Scheme 90b). Thus, the aerobic annulation of alkyne **59k** by benzamide **85l** through the C−H/N−H functionalization set the stage for a step-economical access to the anticancer agent 21,22-dimethoxyrosettacin[133] **170** among others. Here, the unique reactivity of the cobalt-catalyzed oxidative annulation with terminal alkynes was essential, avoiding tedious reaction sequences for the installation and removal of a silyl protecting group on the alkyne moiety.[134]

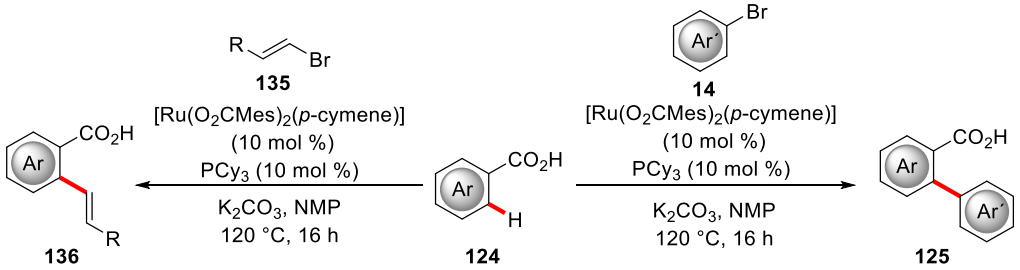


Scheme 90. Product diversification: (a) Traceless removal of PyO and (b) Step economical synthesis of 21,22-dimethoxyrosettacin.

4 Summary and Outlook

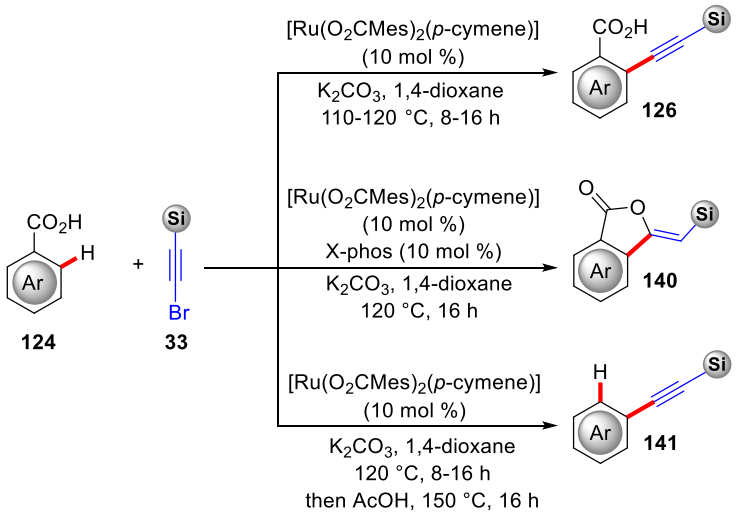
Catalytic C−H functionalization has emerged as an economically-attractive and environmentally-benign alternative to conventional cross-coupling approaches. Thus, major efforts have been made on transformations of inert C–H bonds into useful functionalities. The work presented within this thesis mainly focused on the development and application of versatile ruthenium- and cobalt-catalyzed direct C−H functionalizations.

In the first project, a phosphine-modified ruthenium(II) biscarboxylate catalyst enabled C–H arylations of benzoic acids with excellent positional selectivity and ample substrates scope. Importantly, the unique synthetic utility of the ruthenium(II) catalysis regime also set the stage for site-selective C–H olefinations of benzoic acids (Scheme 91).



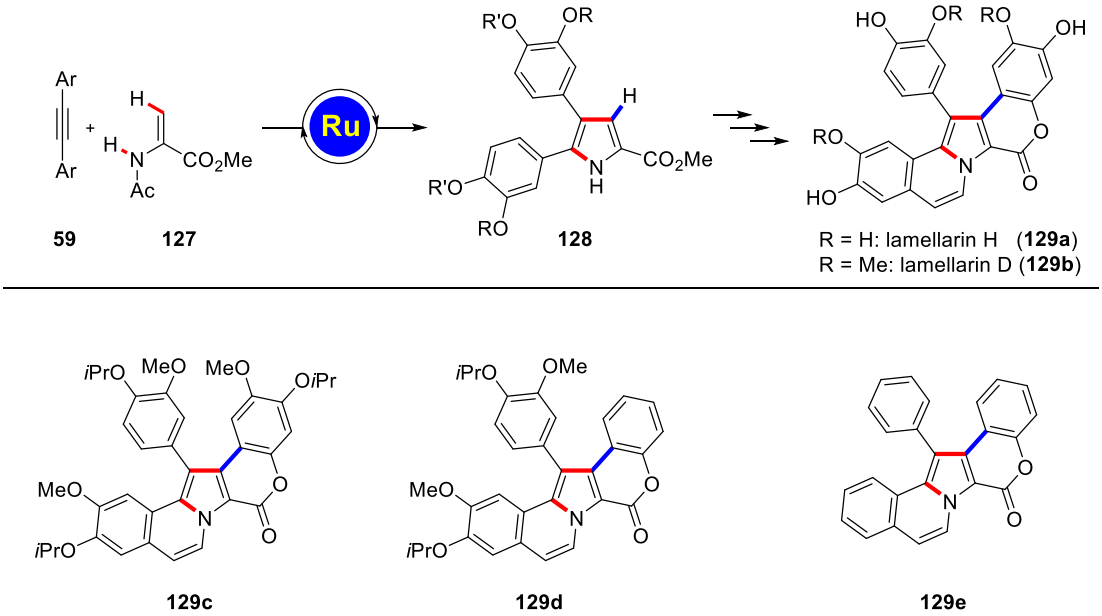
Scheme 91. Ruthenium(II)-catalyzed C–H arylation and olefination of benzoic acids.

Inspired by the above mentioned robustness of C–H arylations and olefination of benzoic acids protocol, we subsequently achieved the first ruthenium-catalyzed C–H alkynylation of weakly-*O*-coordinating substrates. The reaction proceeded under mild conditions with the weak base K_2CO_3. The versatility of the ruthenium(II) catalysis was illustrated by providing step-economical access to phthalides as well as enabling unprecedented decarboxylative *ortho*-C−H alkynylations (Scheme 92).



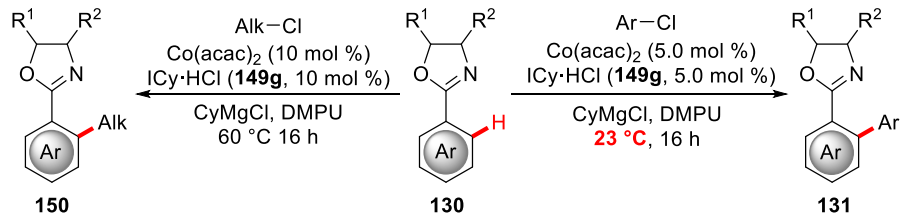
Scheme 92. Ruthenium(II)-catalyzed C–H alkynylations of weakly coordinating benzoic acids.

In the third project, we investigated the efficiency of various transition metal catalysts in the C–H/N–H activation of enamides for the step-economical synthesis of lamellarin alkaloids. Thus, the inexpensive ruthenium(II) catalyst proved to be particularly effective for the key oxidative alkyne annulation, which provided modular access to the naturally-occurring alkaloids lamellarin D and H (**129a-b**) as well as truncated derivatives **129c-e** (Scheme 93).



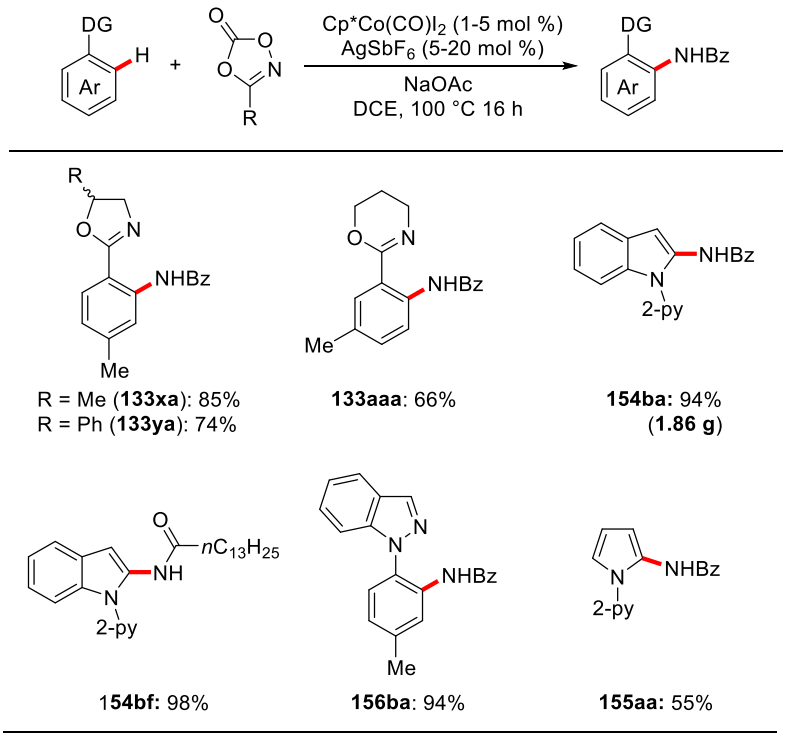
Scheme 93. Modular synthesis of lamellarin alkaloids by C–H/N–H functionalizations.

Subsequently, we disclosed the first low valent cobalt-catalyzed C–H arylation and C–H alkylation by oxazoline assistance (Scheme 94). Thus, cobalt catalysts derived from *N*-heterocyclic carbenes enabled positional-selective C–H arylations and alkylation with inexpensive aryl/alkyl chlorides as electrophiles. Thereby, biaryl oxazolines were prepared in a step-economical fashion, which thus far required the use of precious metal catalysts. Mechanistic studies suggested a facile C–H metalation and a kinetically relevant C–Cl cleavage. Importantly, the obtained biarylated imidates could be easily transformed to a variety of valuable functionalities, which gave expedient access to key structural scaffold of bioactive compounds.



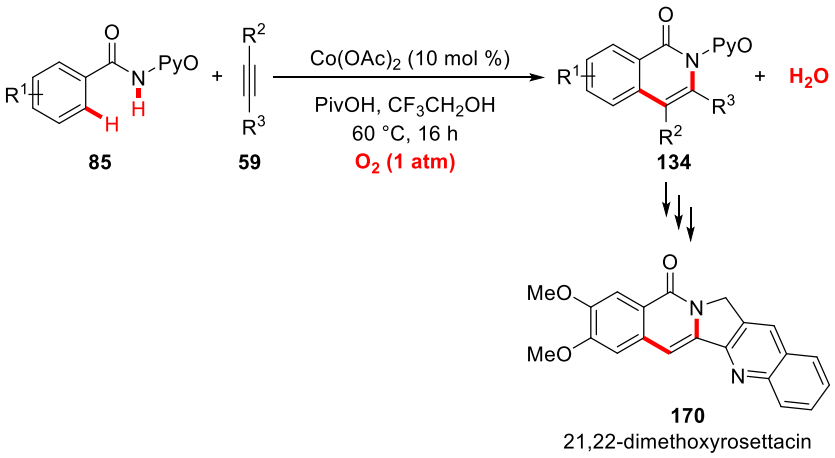
Scheme 94. Cobalt-catalyzed C−H arylation and C−H alkylation by oxazoline assistance.

Thereafter, we reported the first cobalt-catalyzed C−H amidation by the assistance of synthetically useful oxazolines. Thus, a versatile cobalt(III) catalyst allowed for the direct amidation using robust dioxazolones with ample substrate scope, which also proved viable to C−H functionalizations on indoles, pyrroles, pyrozoles as well as phenyl pyridines. The synthetic utility of the oxazolinyl-assisted C−H amidation proctol was further demonstrated by late-stage diversification and large scale reaction. Mechanistic studies provided strong support for a kinetically relevant C−H cobaltation by carboxylate assistance (Scheme 95).



Scheme 95. Cobalt-catalyzed C−H amidation.

Finally, described herein is the unprecedented cobalt-catalyzed oxidative alkyne annulation by C−H/N−H functionalizations with O_2 as the sole oxidant. Thus, by utilizing inexpensive $Co(OAc)_2$ as the catalyst, isoquinolones were accessed in a step-economical fashion with both terminal and internal alkynes under extremely mild conditions. The practical importance of the cobalt oxidase catalysis was illustrated by an efficient synthesis of a cytotoxic topoisomerase-I inhibitor **170** (Scheme 96).



Scheme 96. Cobalt-catalyzed oxidase C−H functionalization.

5 Experimental Section

5.1 General Remarks

Unless otherwise noted, all reactions were performed under an argon or nitrogen atmosphere using pre-dried glassware and standard Schlenk techniques.

Solvents

All solvents for reactions involving moisture-sensitive reagents were dried, distilled and stored under an inert atmosphere (argon or nitrogen) according to the following standard procedures.

1,2-Dimethoxyether (DME) and ***tert*-amylalcohol** (*t*-AmOH) were used as supplied by Merck or stirred over sodium chips for 5 h at 120 °C and then distilled at ambient pressure.

Water (H_2O) was degassed before its use, applying repeated freeze-pump-thaw degassing procedure.

1,2-Dichloroethane (DCE) and **1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone** (DMPU) were dried over CaH_2 for 8 h, degassed and distilled under reduced pressure.

Dichloromethane (DCM), ***N*,*N*-dimethylformamide** (DMF) and **tetrahydrofuran** (THF) were purified using a solvent purification system (SPS) from Mbraun.

***N*-Methyl-2-pyrrolidone** (NMP) was dried over CaH_2 for 4 h at 150 °C and subsequently distilled under reduced pressure.

Methanol (MeOH) was distilled from magnesium methanolate.

Toluene was pre-dried over KH followed by distillation from sodium benzophenone.

1,4-Dioxane was dried over sodium, benzophenone and distilled afterwards.

Vacuum

The following pressures were measured on the used vacuum pump and were not corrected: membrane pump vacuum (MPV): 0.5 mbar, oil pump vacuum (OPV): 0.1 mbar.

Melting Points (M. p.)

Melting points were measured, using a Stuart® Melting Point Apparatus SMP3 from Barloworld scientific. Reported values are uncorrected.

Chromatography

Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60F-plates (Merck) with 254 nm fluorescent indicator from Merck. Plates were visualized under UV-light or developed by treatment with a $KMnO_4$ solution followed by carefully heating. Chromatographic purification of products was

accomplished by flash column chromatography on MERCK silica gel, grade 60 (0.040–0.063 mm and 0.063–0.200 mm).

Gas Chromatography (**GC**)

The conversion of the reactions was monitored by coupled gas chromatography/mass spectrometry using *G1760C GCDplus* with mass detector *HP 5971, 5890 Series II* with mass detector *HP 5972* from HEWLETT-PACKARD and *7890A GC-System* with mass detector *5975C (Triplex-Axis-Detector)* from AGILENT TECHNOLOGIES equipped with *HP-5MS* columns (30 m × 0.25 mm, *Ø* 0.25 m).

High Performance Liquid Chromatography (**HPLC**)

Preparative and analytical separations were performed on an HPLC-System from KNAUER (*Smartline Pump 100*, Dynamic Mixing Chamber, Injection-and Control-Valve, *Smartline UV Detector 2500*). Separation normal phase column (250×10 mm) from MACHEREY-NAGEL (MN) was used. Organic solvents of HPLC grade were employed. All samples were filtered through Polytetrafluoroethylene Filter from ROTH (*Ø* 25 mm, 0.2 μm) or VWR (*Ø* 13 mm, 0.2 μm) prior to separation.

Nuclear Magnetic Resonance Spectroscopy (**NMR**)

Nuclear magnetic resonance (NMR) spectroscopy was performed at 300, 400, 500 or 600 MHz (^{1}H NMR), 75, 100 or 125 MHz (^{13}C NMR, APT) and 283 MHz or 471 MHz (^{19}F NMR) on BRUKER *AM* 250, VARIAN *Unity-300* and *Inova 500* instruments. Chemical shifts were reported as δ-values in ppm relative to the residual proton peak of the deuterated solvent or its carbon atom, respectively, or the standard trimethylsilyl (TMS) peak. For characterization of the observed resonance multiplicities the following abbreviations were applied: *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *m* (multiplet), *dd* (doublet of doublet), *dt* (doublet of triplet), or analogue representations. The coupling constants *J* are reported in Hertz (Hz).

Infrared Spectroscopy (**IR**)

Infrared spectra were recorded on a Bruker *Alpha-P* ATR-spectrometer. Liquid probes have been measured as films between the plates of NaCl and solid probes neat applying Attenuated Total Reflection (ATR) technique which enabled the samples to be examined directly. Analysis of the spectral data has been done by using the *OPUS 3.1* software from Bruker, respectively *OPUS 6*. Absorption ($\tilde{\nu}$) was given in wave numbers (cm^{-1}). Spectra were recorded in the range of 4000 to 400 cm^{-1}.

Mass Spectrometry (**MS**)

MS (EI) and HR-MS (EI) were measured on a *Time-of-Flight* mass spectrometer AccuTOF from JOEL. ESI-mass spectra were recorded on an *Ion-Trap* mass spectrometer *LCQ* from FINNIGAN or on a *Time-of-Flight* mass spectrometer *microTOF* from BRUKER. ESI-HR-MS spectra were recorded on a BRUKER *APEX IV* or a *BRUKER DALTONIC* {7T, Fourier Transform Ion Cyclotron Resonance (FTICR)} mass spectrometer. The

ratios of mass to charge (*m/z*) were indicated, intensities relative to the base peak (I = 100) were written in parentheses.

Reagents

Chemicals obtained from commercial sources with purity above 95% were used without further purification. The following compounds are known and were synthesized according to previously described methods: $[RuCl_2(p\text{-cymene})(PCy_3)]$,[135] ruthenacycle **137a**,[132b] (bromoethynyl)triisopropylsilane **32a**,[136] methyl 2-acetamidoacrylate,[137] 2-aryl oxazolines and 2-aryl oxazines **130a-aa**,[138] N-heterocyclic carbene (NHC) preligands **149a-149i**,[139] dioxazolones **132a-f**,[140] $[Cp^*CoI_2(CO)]$,[83] $[Cp^*CoI_2]_2$,[141] $[Cp^*Co(MeCN)_3](SbF_6)_2$,[86] amides **85a-l**,[142] **[D]$_5$-85b**,[142] **[D]$_1$-85b**.[143]

The following compounds were obtained by the generous courtesy of the persons named below:

Karsten Rauch: $[Ru(O_2CMes)_2(p\text{-cymene})]$, $[RuCl_2(p\text{-cymene})]_2$.

M. Sc. Joachim Loup: $[CpCoI_2(CO)]$.

Dr. Svenja Warratz: $[RuCl_2(p\text{-cymene})(PhtBuPOH)]$.

M. Sc. Torben Rogge: $[RuCl_2(p\text{-cymene})(nBu_2POH)]$.

M. Sc. Zhixiong Ruan: (Bromoethynyl)(*tert*-butyl)dimethylsilane **32b**.

Dr. Weiping Liu: (Pyridin-2-yl)-1*H*-indoles and (pyrimidin-2-yl)-1*H*-indoles **102b-g**.

M. Sc. Qingqing Bu: 2-(1*H*-Pyrrol-1-yl)pyridine **155a**.

5.2 General Procedures

General Procedure A for Ruthenium(II)-Catalyzed C–H Arylations of Benzoic Acids with Aryl Halides by Weak-*O*-Coordination

A suspension of $[Ru(O_2CMes)_2(p\text{-cymene})]$ (**16**) (28.1 mg, 10 mol %), PCy_3 (14.0 mg, 10 mol %), K_2CO_3 (138 mg, 1.00 mmol), **124** (0.50 mmol), and **14** (0.75 mmol, 1.50 equiv) in NMP (2.0 mL) was stirred under N_2 for 16 h at 120 °C. At ambient temperature, MeCN (3.0 mL), K_2CO_3 (207 mg, 1.50 mmol) and MeI (355 mg, 2.50 mmol) were added and the mixture was stirred at 50 °C for another 2 h. After cooling to ambient temperature, the mixture was diluted with MTBE (120 mL), then washed with H_2O (20 mL) and brine (20 mL) sequentially. The organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to yield the methyl esters **125**.

General Procedure B for Ruthenium(II)-Catalyzed C−H Alkynylation of Weakly Coordinating Benzoic Acids

A suspension of [$Ru(O_2CMes)_2$(*p*-cymene)] (**16**) (28.1 mg, 10 mol %), K_2CO_3 (138 mg, 1.00 mmol), **124** (0.50 mmol), and **33** (0.65 mmol, 1.30 equiv) in 1,4-dioxane (1.0 mL) was stirred under N_2 for 16 h at 120 ºC. At ambient temperature, MeCN (3.0 mL), K_2CO_3 (138 mg, 1.0 mmol) and MeI (355 mg, 2.50 mmol) were added and the mixture was stirred at 50 ºC for additional 2 h. At ambient temperature, the mixture was dry-loaded onto silica gel and purified by column chromatography (*n*-hexane/EtOAc) and HPLC (when required) to give products **126**.

General Procedure C for Ruthenium(II)-Catalyzed C–H Alkynylation of Benzoic Acids: Access to Free Acids 126´

A suspension of [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %), K_2CO_3 (138 mg, 1.00 mmol), benzoic acid **124** (0.50 mmol), and alkynyl bromide **33** (0.65 mmol, 1.30 equiv) in 1,4-dioxane (1.0 mL) was stirred under N_2 for 16 h at 120 ºC. At ambient temperature, AcOH (2.0 mL) was added, the mixture was dry-loaded onto silica gel and purified by column chromatography (*n*-hexane/EtOAc/AcOH) to give products **126´**.

General procedure D for Cobalt-Catalyzed C–H Functionalizations by Imidate Assistance with Aryl and Alkyl Chlorides

A suspension of $Co(acac)_2$ (6.4 mg, 5.0 mol %), ICy·HCl (**149g**) (6.7 mg, 5.0 mol %), **130** (0.50 mmol, 1.0 equiv), **8** (0.65 mmol, 1.3 equiv) and DMPU (1.0 mL) was stirred for 5 min at 0 °C. A solution of CyMgCl in 2-Me-THF (1.0 M, 1.0 mL, 2.0 equiv) was added dropwise at the same temperature. Then the mixture was stirred at 23 °C for 16 h. At ambient temperature, aq. NH_4Cl (2.0 mL) and H_2O (15 mL) were added. The reaction mixture was extracted with MTBE (3 × 20 mL). The combined organic phase was washed with brine (20 mL) and dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification of the remaining residue by column chromatography on silica gel (*n*-hexane/EtOAc 5/1) yielded product **131**.

General Procedure E for the Amidation of 2-Phenyloxazolines

2-Phenyloxazolines **130** (0.50 mmol, 1.0 equiv), dioxazolones **132** (0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (0.025 mmol, 5.0 mol %), $AgSbF_6$ (0.10 mmol, 20 mol %) and NaOAc (0.10 mmol, 20 mol %) were placed into a 25 mL Schlenk tube equipped with a septum under N_2 atmosphere. DCE (2.0 mL) was introduced *via* cannula. The reaction mixture was stirred at 100 °C for 16 h. After cooling to ambient temperature, the reaction mixture was dry loaded onto silica gel and purified by flash column chromatography (*n*-hexane/EtOAc) to afford the desired products **133**.

General Procedure F for the Amidation of Indoles, Pyrroles, Phenyl Pyridines and Phenyl Pyrazoles

Indoles or pyrroles **102** (0.50 mmol, 1.0 equiv), dioxazolone **132** (0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (0.0125 mmol, 2.5 mol %), $AgSbF_6$ (0.025 mmol, 5.0 mol %) and NaOAc (0.025 mmol, 5.0 mol %) were placed into a 25 mL Schlenk tube equipped with a septum under N_2 atmosphere. DCE (2.0 mL) was introduced *via* cannula. The reaction mixture was stirred at 70 °C for 16 h. After cooling to ambient temperature, the reaction mixture was dry loaded onto silica gel and purified by flash column chromatography (*n*-hexane/EtOAc) to afford the desired product **154**.

General Procedures G for the Cobalt-Catalyzed Oxidase C−H/N−H Alkyne Annulation

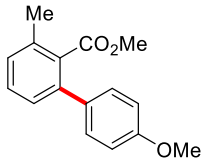
Under an atmosphere of ambient air, aromatic amides **85** (0.50 mmol, 1.0 equiv), alkynes **59** (0.60 mmol, 1.2 equiv), PivOH (102 mg, 1.0 mmol, 2 equiv), and $Co(OAc)_2$ (8.9 mg, 10 mol %) were placed in a Schlenk tube. The Schlenk tube was evacuated and refilled with O_2 three times with a balloon. TFE (2.0 mL) was added *via* a cannula. Then the mixture was stirred in a pre-heated (60 ºC) oil bath for 16 h (with the O_2 balloon being connected to the Schlenk tube). At ambient temperature, the reaction was stopped by adding saturated aqueous $NaHCO_3$ (15 mL). This mixture was extracted with CH_2Cl_2 (4×10 mL), and dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography on silica gel afforded the corresponding products.

General Procedure H for the Cobalt-Catalyzed Annulation, and Subsequent *N*-Deoxygenation with PCl_3

Under an atmosphere of ambient air, aromatic amides **85** (0.50 mmol, 1.0 equiv), alkynes **59** (0.60 mmol, 1.2 equiv), PivOH (102 mg, 1.0 mmol, 2 equiv) and $Co(OAc)_2$ (8.9 mg, 10 mol %) were placed in a Schlenk tube. The Schlenk tube was evacuated and refilled with O_2 three times with a balloon. TFE (2.0 mL) was added *via* cannula. Then the mixture was stirred in a pre-heated (60 ºC) oil bath for 16 h (with the O_2 balloon being connected to the Schlenk tube). At ambient temperature, the solvent was removed in *vacuo*. Under a N_2 atmosphere, the residue was suspended in toluene (5.0 mL), and PCl_3 (83 mg, 1.20 equiv) was added. The mixture was stirred at 50 ºC for 30 min. At ambient temperature, the reaction was stopped by adding saturated aqueous $NaHCO_3$ (15 mL) and stirred for 15 min until the solution was clear. This mixture was extracted with CH_2Cl_2 (4×10 mL), and the combined organic phase was dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography on silica gel using *n*-hexane/EtOAc yielded the corresponding products.

5.3 Experimental Procedures and Analytical Data

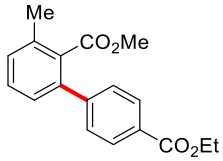
5.3.1 Ruthenium(II)-Catalyzed C–H Arylations of Benzoic Acids with Aryl Halides by Weak-*O*-Coordination



Methyl 4'-methoxy-3-methyl-[1,1'-biphenyl]-2-carboxylate (125aa): The general procedure **A** was followed using benzoic acid **124a** (68 mg, 0.50 mmol) and aryl bromide **14a** (140 mg, 0.75 mmol, 1.5 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125aa** (111 mg, 87%) as a white solid.

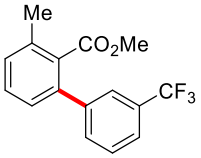
M. p. = 69−70 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.35–7.25 (m, 3H), 7.21–7.14 (m, 2H), 6.91 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H), 3.61 (s, 3H), 2.37 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 170.5 (C_q), 159.0 (C_q), 139.6 (C_q), 135.3 (C_q), 133.3 (C_q), 133.2 (C_q), 129.3 (CH), 129.3 (CH), 128.7 (CH), 127.2 (CH), 113.7 (CH), 55.2 (CH_3), 51.8 (CH_3), 19.7 (CH_3). **IR** (ATR): 2946, 2837, 1724, 1510, 1245, 1028, 791 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 256 (100) [M^+], 225 (90), 209 (30), 197 (15), 182 (30), 153 (40). **HR-MS** (EI) *m/z* calcd for $C_{16}H_{16}O_3$ [M^+] 256.1099, found 256.1109.

The analytical data are in accordance with those previously reported in the literature.[111b]



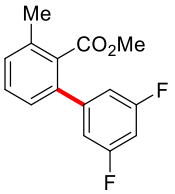
4'-Ethyl 2-methyl 3-methyl-[1,1'-biphenyl]-2,4'-dicarboxylate (125ab): The general procedure **A** was followed using benzoic acid **124a** (68 mg, 0.50 mmol) and aryl bromide **14b** (172 mg, 0.75 mmol, 1.5 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125ab** (134 mg, 90%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.05 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.3 Hz, 2H), 7.36–7.31 (m, 1H), 7.26–7.12 (m, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.55 (s, 3H), 2.38 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 169.8 (C_q), 166.3 (C_q), 145.4 (C_q), 139.1 (C_q), 135.7 (C_q), 132.9 (C_q), 129.7 (CH), 129.4 (CH), 129.4 (C_q), 129.3 (CH), 128.1 (CH), 126.9 (CH), 60.9 (CH_2), 51.8 (CH_3), 19.6 (CH_3), 14.2 (CH_3). **IR** (ATR): 2981, 2950, 1712, 1610, 1460, 1366, 1100, 766 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 298 (100) [M^+], 267 (30), 253 (80), 239 (20), 225 (20), 195 (80), 165 (60). **HR-MS** (EI) *m/z* calcd for $C_{18}H_{18}O_4$ [M^+] 298.1205, found 298.1210.



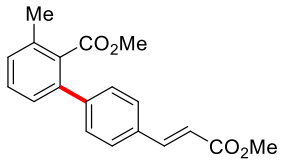
Methyl 3-methyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylate (125ac): The general procedure **A** was followed using benzoic acid **124a** (68 mg, 0.50 mmol) and aryl bromide **14c** (169 mg, 0.75 mmol, 1.5 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125ac** (115 mg, 78%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.66–7.44 (m, 4H), 7.37 (dd, J = 7.6, 7.6 Hz, 1H), 7.28–7.18 (m, 2H), 3.60 (s, 3H), 2.40 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 169.8 (C_q), 141.6 (C_q), 138.6 (C_q), 135.8 (C_q), 133.2 (C_q), 131.6 (q, $^{4}J_{C\text{-}F}$ = 1.3 Hz, CH), 130.7 (q, $^{2}J_{C\text{-}F}$ = 32.2 Hz, C_q), 129.8 (CH), 129.6 (CH), 128.8 (CH), 127.1 (CH), 125.0 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz, CH), 124.1 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz, CH), 124.0 (q, $^{1}J_{C\text{-}F}$ = 272.3 Hz, C_q), 124.0, 51.8 (CH_3), 19.7 (CH_3). **^{19}F NMR** (283 MHz, $CDCl_3$) δ = -62.6 (s). **IR** (ATR): 2949, 1729, 1483, 1334, 1118, 1065, 703 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 294 (40) [M^+], 263 (100), 243 (5), 235 (10), 215 (20), 193 (5), 165 (40). **HR-MS** (EI) *m/z* calcd for $C_{16}H_{13}F_3O_2$ [M^+] 294.0868, found 294.0866.



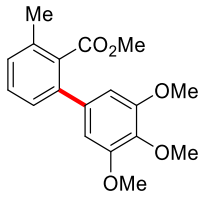
Methyl 3',5'-difluoro-3-methyl-[1,1'-biphenyl]-2-carboxylate (125ad): The general procedure **A** was followed using benzoic acid **124a** (68 mg, 0.50 mmol) and aryl bromide **14d** (145 mg, 0.75 mmol, 1.5 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125ad** (110 mg, 84%) as a colorless solid.

M. p. = 63−64 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.37 (dd, J = 7.6, 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 6.96–6.85 (m, 2H), 6.83–6.75 (m, 1H), 3.67 (s, 3H), 2.40 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 169.6 (C_q), 162.7 (dd, $^{1,3}J_{C\text{-}F}$ = 248.7, 13.0 Hz, C_q), 144.1 (t, $^{3,3}J_{C\text{-}F}$ = 25.3 Hz, C_q), 137.8 (t, $^{4,4}J_{C\text{-}F}$ = 2.4 Hz, C_q), 135.8 (C_q), 132.9 (C_q), 130.1 (CH), 129.6 (CH), 126.8 (CH), 111.3 (dd, $^{2,4}J_{C\text{-}F}$ = 17.3, 8.1 Hz, CH), 102.8 (t, $^{2,2}J_{C\text{-}F}$ = 25.3 Hz, CH), 52.0 (CH_3), 19.7 (CH_3). **^{19}F NMR** (283 MHz, $CDCl_3$) δ = -(109.8–109.9) (m). IR (ATR): 2951, 1726, 1622, 1454, 1337, 1117, 793 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 262 (60) [M^+], 231 (100), 253 (80), 201 (60), 188 (30), 183 (50), 151 (50). **HR-MS** (ESI) *m/z* calcd for $C_{15}H_{13}F_2O_2$ [M+H^+] 263.0878, found 263.0875.



Methyl (*E*)-4'-(3-methoxy-3-oxoprop-1-en-1-yl)-3-methyl-[1,1'-biphenyl]-2-carboxylate (125ae): The general procedure **A** was followed using benzoic acid **124a** (68 mg, 0.50 mmol) and aryl bromide **14e** (181 mg, 0.75 mmol, 1.5 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125ae** (126 mg, 81%) as a colorless solid.

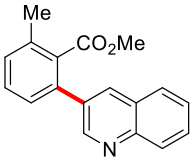
M. p. = 91−92 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 16.0 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.41–7.31 (m, 3H), 7.28–7.18 (m, 2H), 6.47 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 3H), 3.60 (s, 3H), 2.40 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 169.9 (C_q), 167.2 (C_q), 144.2 (CH), 142.9 (C_q), 139.1 (C_q), 135.6 (C_q), 133.3 (C_q), 132.9 (C_q), 129.5 (CH), 129.4 (CH), 128.7 (CH), 128.0 (CH), 126.9 (CH), 117.8 (CH), 51.8 (CH_3), 51.6 (CH_3), 19.6 (CH_3). **IR** (ATR): 2944, 1729, 1708, 1604, 1436, 1270, 1170, 790 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 310 (80) [M^+], 278 (50), 247 (100), 219 (50), 189 (40), 165 (30). HR-MS (ESI) *m/z* calcd for $C_{19}H_{18}O_4$ [$M+H^+$] 310.1205, found 310.1214.



Methyl 3',4',5'-trimethoxy-3-methyl-[1,1'-biphenyl]-2-carboxylate (125af): The general procedure **A** was followed using benzoic acid **124a** (68 mg, 0.50 mmol) and aryl bromide **14f** (185 mg, 0.75 mmol, 1.5 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125af** (133 mg, 84%) as a colorless oil.

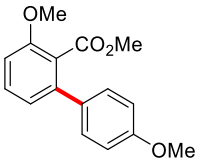
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.35–7.30 (m, 1H), 7.25–7.16 (m, 2H), 6.57 (s, 2H), 3.86 (s, 3H), 3.84 (s, 6H), 3.62 (s, 3H), 2.36 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 170.4 (C_q), 153.0 (C_q), 139.9 (C_q), 137.3 (C_q), 136.4 (C_q), 135.3 (C_q), 133.1 (C_q), 129.3 (CH), 129.1 (CH), 126.9 (CH), 105.4 (CH), 60.9 (CH_3), 56.0 (CH_3), 52.0 (CH_3), 19.6 (CH_3). **IR** (ATR): 2942, 2836, 1723, 1577, 1462, 1405, 1120 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 316 (100) [M^+], 301 (80), 285 (10), 273 (15), 241 (10), 209 (10), 199 (10). **HR-MS** (EI) *m/z* calcd for $C_{18}H_{20}O_5$ [$M+H^+$] 316.1311, found 316.1301.

The analytical data are in accordance with those previously reported in the literature.[111b]



Methyl 2-methyl-6-(quinolin-3-yl)benzoate (125ag): The general procedure **A** was followed using benzoic acid **124a** (68 mg, 0.50 mmol), aryl bromide **14g** (156 mg, 0.75 mmol, 1.5 equiv) and NaI (150 mg, 1.00 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125ag** (46 mg, 33%) as a colorless oil.

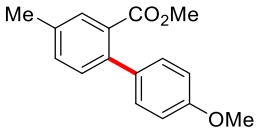
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.92 (s, 1H), 8.14–8.12 (m, 2H), 7.83 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.74–7.70 (m, 1H), 7.56 (dd, *J* = 8.2, 6.9 Hz, 1H), 7.44–7.40 (m, 1H), 7.30–7.27 (m, 2H), 3.56 (s, 3H), 2.43 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 169.7 (C_q), 150.3 (CH), 147.1 (C_q), 136.5 (C_q), 136.1 (C_q), 134.7 (CH), 133.8 (C_q), 133.5 (C_q), 130.0 (CH), 129.8 (CH), 129.6 (CH), 129.2 (CH), 128.0 (CH), 127.6 (CH), 127.6 (C_q), 127.0 (CH), 52.0 (CH_3), 19.8 (CH_3). **IR** (ATR): 3063, 2949, 2855, 1721, 1490, 1435, 1264, 1084 cm^{-1}. **HR-MS** (ESI) *m/z* calcd for $C_{18}H_{16}NO_2$ [M+H$^+$] 278.1176, found 278.1182.



Methyl 3,4'-dimethoxy-[1,1'-biphenyl]-2-carboxylate (125ba): The general procedure **A** was followed using benzoic acid **124b** (76 mg, 0.50 mmol) and aryl bromide **14a** (140 mg, 0.75 mmol, 1.5 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125ba** (79 mg, 58%) as a colorless solid.

M. p. = 92−93 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.43–7.29 (m, 3H), 6.99–6.88 (m, 4H), 3.87 (s, 3H), 3.83 (s, 3H), 3.66 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.7 (C_q), 159.2 (C_q), 156.4 (C_q), 140.8 (C_q), 132.4 (C_q), 130.4 (CH), 129.3 (CH), 123.0 (C_q), 121.9 (CH), 113.8 (CH), 109.5 (CH), 56.0 (CH_3), 55.2 (CH_3), 52.1 (CH_3). **IR** (ATR): 2959, 2860, 1726, 1464, 1238, 1102, 1018, 791 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 272 (90) [M$^+$], 241 (100), 226 (40), 211 (15), 198 (20), 183 (15), 168 (10). **HR-MS** (EI) *m/z* calcd for $C_{16}H_{16}O_4$ [M$^+$] 272.1049, found 272.1045.

The analytical data are in accordance with those previously reported in the literature.[111b]

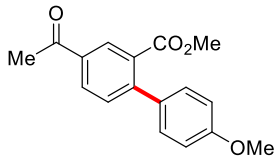


Methyl 4'-methoxy-4-methyl-[1,1'-biphenyl]-2-carboxylate (125ca): The general procedure **A** was followed using benzoic acid **124c** (68 mg, 0.50 mmol) and aryl bromide **14a** (140 mg, 0.75 mmol, 1.5 equiv).

Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125ca** (86 mg, 67%) as a colorless oil.

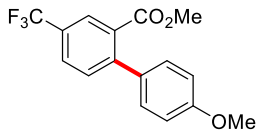
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50 (dd, *J* = 1.3, 0.6 Hz, 1H), 7.29–7.04 (m, 4H), 6.82 (d, *J* = 8.7 Hz, 2H), 3.73 (s, 3H), 3.56 (s, 3H), 2.30 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 169.4 (C_q), 158.8 (C_q), 139.1 (C_q), 136.5 (C_q), 133.5 (C_q), 131.8 (CH), 130.6 (C_q), 130.5 (CH), 130.1 (CH), 129.4 (CH), 113.4 (CH), 55.1 (CH_3), 51.8 (CH_3), 20.8 (CH_3). **IR** (ATR): 2948, 2836, 1715, 1609, 1488, 1289, 1238, 821 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 256 (100) [M^+], 225 (80), 210 (10), 197 (15), 182 (20), 165 (15), 153 (20). **HR-MS** (EI) *m/z* calcd for $C_{16}H_{16}O_3$ [M^+] 256.1099, found 256.1091.

The analytical data are in accordance with those previously reported in the literature.[111b]



Methyl 4-acetyl-4'-methoxy-[1,1'-biphenyl]-2-carboxylate (125da): The general procedure **A** was followed using benzoic acid **124d** (82 mg, 0.50 mmol) and 1-iodo-4-methoxybenzene (**14a'**) (175 mg, 0.75 mmol, 1.5 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125da** (115 mg, 81%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.32 (dd, *J* = 1.9, 0.5 Hz, 1H), 8.05 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.44 (dd, *J* = 8.1, 0.5 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 3.68 (s, 3H), 2.62 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 196.8 (C_q), 168.6 (C_q), 159.5 (C_q), 146.3 (C_q), 135.3 (C_q), 132.3 (C_q), 131.1 (C_q), 131.0 (CH), 130.5 (CH), 129.9 (CH), 129.4 (CH), 113.7 (CH), 55.2 (CH_3), 52.2 (CH_3), 26.6 (CH_3). **IR** (ATR): 2950, 2837, 1719, 1682, 1602, 1518, 1226, 826 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 284 (90) [M^+], 269 (100), 253 (20), 241 (10), 226 (20), 211 (15), 195 (10). **HR-MS** (EI) *m/z* calcd for $C_{17}H_{16}O_4$ [M^+] 284.1049, found 284.1043.

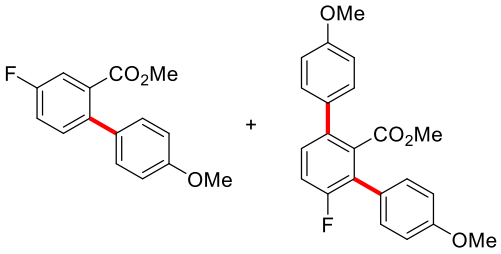


Methyl 4'-methoxy-4-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylate (125ea): The general procedure **A** was followed using benzoic acid **124e** (95 mg, 0.50 mmol) and 1-iodo-4-methoxybenzene (**2a'**) (175 mg, 0.75 mmol, 1.5 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125ea** (140 mg, 90%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.04 (dd, *J* = 1.4, 0.7 Hz, 1H), 7.73 (ddd, *J* = 8.1, 2.0, 0.8 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 3.84 (s, 3H), 3.69 (s, 3H). **^{13}C NMR** (75

MHz, $CDCl_3$) δ = 168.0 (C_q), 159.5 (C_q), 145.5 (q, $^4J_{C-F}$ = 1.6 Hz, C_q), 132.1 (C_q), 131.3 (C_q), 131.3 (CH), 129.4 (CH), 129.1 (q, $^2J_{C-F}$ = 33.1 Hz, C_q), 127.7 (q, $^3J_{C-F}$ = 3.6 Hz, CH), 126.8 (q, $^3J_{C-F}$ = 3.8 Hz, CH), 123.7 (q, $^1J_{C-F}$ = 272.3 Hz, C_q), 113.8 (CH), 55.2 (CH_3), 52.3 (CH_3). **^{19}F NMR** (283 MHz, $CDCl_3$) δ = - 62.6 (s). **IR** (ATR): 2952, 2839, 1726, 1609, 1522, 1334, 1240, 1081 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 310 (100) [M^+], 279 (90), 264 (10), 251 (15), 236 (20), 207 (10), 188 (10). **HR-MS** (EI) *m/z* calcd for $C_{16}H_{13}F_3O_3$ [M^+] 310.0817, found 310.0821.

The analytical data are in accordance with those previously reported in the literature.[111b]



The general procedure **A** was followed using benzoic acid **124f** (70 mg, 0.50 mmol) and 1-iodo-4-methoxybenzene (**14a'**) (175 mg, 0.75 mmol, 1.5 equiv) and K_2CO_3 (138 mg, 1.00 mmol, 2.0 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125fa** (Colorless oil, 73 mg, 56%) and the diarylated product **125fa'** (Pale yellow solid, 16 mg, 9%).

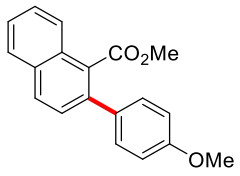
Methyl 4-fluoro-4'-methoxy-[1,1'-biphenyl]-2-carboxylate (125fa):

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.32 (dd, *J* = 8.5, 5.5 Hz, 1H), 7.24–7.17 (m, 3H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 3.68 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 167.9 (d, $^4J_{C-F}$ = 2.4 Hz, C_q), 161.3 (d, $^1J_{C-F}$ = 247.3 Hz, C_q), 159.0 (C_q), 138.2 (d, $^4J_{C-F}$ = 3.4 Hz, C_q), 132.6 (C_q), 132.4 (d, $^3J_{C-F}$ = 7.6 Hz, CH), 132.2 (d, $^3J_{C-F}$ = 7.3 Hz, C_q), 129.4 (CH), 118.1 (d, $^2J_{C-F}$ = 21.1 Hz, CH), 116.5 (d, $^2J_{C-F}$ = 23.4 Hz, CH), 113.5 (CH), 55.2 (CH_3), 52.1 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -(115.3–115.4) (m). **IR** (ATR): 2951, 2837, 1718, 1608, 1484, 1235, 1175, 822 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 261 (30) [M+H^+], 260 [M^+] (100), 245 (10), 229 (80), 214 (15), 186 (30). **HR-MS** (EI) *m/z* calcd for $C_{15}H_{13}FO_3$ [M^+] 260.0849, found 260.0857.

Methyl 4'-fluoro-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-carboxylate (125fa'):

M. p. = 121−122 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.34–7.27 (m, 5H), 7.23–7.20 (m, 1H), 6.96–6.92 (m, 4H), 3.84 (s, 3H), 3.84 (s, 3H), 3.39 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 168.7 (d, $^4J_{C-F}$ = 3.3 Hz, C_q), 158.7 (d, $^1J_{C-F}$ = 246.1 Hz, C_q), 159.4 (C_q), 159.1 (C_q), 135.7 (d, $^3J_{C-F}$ = 4.1 Hz, C_q), 135.3 (d, $^3J_{C-F}$ = 2.7 Hz, C_q), 132.0 (C_q), 130.6 (d, $^4J_{C-F}$ = 1.4 Hz, CH), 130.2 (d, $^3J_{C-F}$ = 8.2 Hz, CH), 129.5 (CH), 127.3 (d, $^2J_{C-F}$ = 18.1 Hz, C_q) 125.4 (C_q), 116.6 (d, $^2J_{C-F}$ = 23.2 Hz, CH), 113.8 (CH), 113.7 (CH), 55.2 (CH_3), 55.2 (CH_3), 51.9 (CH_3). **^{19}F NMR** (471 MHz, $CDCl_3$) δ = -117.7 (dd, *J* = 9.2, 5.0 Hz). **IR** (ATR): 2935, 2837, 1728, 1608, 1514,

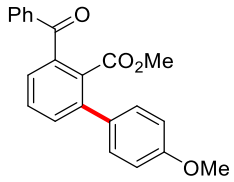
1463, 1250, 822 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 389 (100) [M+Na^+], 335 (10), 278 (5), 219 (10), 203 (5), 149 (5). **HR-MS** (ESI) *m/z* calcd for $C_{22}H_{20}FO_4$ [M+H^+] 367.1340, found 367.1344.



Methyl 2-(4-methoxyphenyl)-1-naphthoate (125ga): The general procedure **A** was followed using benzoic acid **124g** (86 mg, 0.50 mmol) and aryl bromide **14a** (140 mg, 0.75 mmol, 1.5 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125ga** (114 mg, 78%) as a colorless solid.

M. p. = 121−122 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.99–7.85 (m, 3H), 7.63–7.48 (m, 3H), 7.43 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 3.76 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 170.2 (C_q), 159.2 (C_q), 137.5 (C_q), 133.2 (C_q), 132.1 (C_q), 130.0 (C_q), 129.8 (CH), 129.7 (C_q), 129.6 (CH), 128.1 (CH), 127.5 (CH), 127.4 (CH), 126.1 (CH), 124.9 (CH), 113.9 (CH), 55.3 (CH_3), 52.2 (CH_3). **IR** (ATR): 2937, 1727, 1608, 1516, 1429, 1231, 1025, 815 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 292 (98) [M^+], 261 (100), 246 (10), 218 (20), 189 (30), 163 (5), 146 (5). **HR-MS** (EI) *m/z* calcd for $C_{19}H_{16}O_3$ [M^+] 292.1099, found 292.1090.

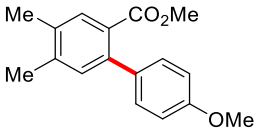
The analytical data are in accordance with those previously reported in the literature.[111b]



Methyl 3-benzoyl-4'-methoxy-[1,1'-biphenyl]-2-carboxylate (125ha): The general procedure **A** was followed using benzoic acid **124h** (113 mg, 0.50 mmol) and aryl bromide **14a** (140 mg, 0.75 mmol, 1.5 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125ha** (92 mg, 53%) as a colorless solid.

M. p. = 108−109 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.91–7.79 (m, 2H), 7.63–7.50 (m, 3H), 7.53–7.42 (m, 3H), 7.31 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 3.45 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 196.4 (C_q), 168.9 (C_q), 159.3 (C_q), 141.2 (C_q), 138.5 (C_q), 136.8 (C_q), 133.1 (CH), 132.8 (CH), 132.7 (C_q), 132.1 (C_q), 130.1 (CH), 129.5 (CH), 129.2 (CH), 128.4 (CH), 127.8 (CH), 113.8 (CH), 55.2 (CH_3), 52.1 (CH_3). **IR** (ATR): 2950, 2841, 1936, 1730, 1606, 1516, 1247, 1050 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 346 (100) [M^+], 315 (60), 297 (10), 269 (40), 237 (20), 181 (15), 215 (10). **HR-MS** (EI) *m/z* calcd for $C_{22}H_{18}O_4$ [M^+] 346.1205, found 346.1194.

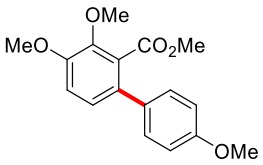
The analytical data are in accordance with those previously reported in the literature.[111b]



Methyl 4'-methoxy-4,5-dimethyl-[1,1'-biphenyl]-2-carboxylate (125ia): The general procedure **A** was followed using benzoic acid **124i** (75 mg, 0.50 mmol) and 1-iodo-4-methoxybenzene (**14a'**) (175 mg, 0.75 mmol, 1.5 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125ia** (112 mg, 83%) as a colorless solid.

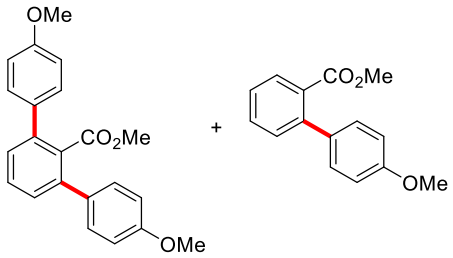
M. p. = 82−83 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.62 (s, 1H), 7.23 (d, J = 8.8 Hz, 2H), 7.13 (s, 1H), 6.93 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.66 (s, 3H), 2.32 (s, 3H), 2.32 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 169.2 (C_q), 158.7 (C_q), 140.3 (C_q), 139.8 (C_q), 135.2 (C_q), 133.8 (C_q), 132.1 (CH), 131.0 (CH), 129.4 (CH), 127.8 (C_q), 113.3 (CH), 55.2 (CH_3), 51.7 (CH_3), 19.7 (CH_3), 19.2 (CH_3). **IR** (ATR): 2951, 1724, 1607, 1488, 1443, 1241, 1026, 834 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 270 (100) [M^+], 239 (90), 224 (15), 211 (15), 196 (30), 181 (15), 165 (15). **HR-MS** (EI) *m/z* calcd for $C_{17}H_{18}O_3$ [M^+] 270.1256, found 270.1247.

The analytical data are in accordance with those previously reported in the literature.[144]



Methyl 3,4,4'-trimethoxy-[1,1'-biphenyl]-2-carboxylate (125ja): The general procedure **A** was followed using benzoic acid **124j** (91 mg, 0.50 mmol) and 1-iodo-4-methoxybenzene (**14a'**) (175 mg, 0.75 mmol, 1.5 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125ja** (141 mg, 93%) as a colorless solid.

M. p. = 106−107 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.27 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.5 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.80 (s, 3H), 3.67 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.2 (C_q), 158.9 (C_q), 151.5 (C_q), 146.0 (C_q), 132.2 (C_q), 132.1 (C_q), 129.2 (CH), 128.7 (C_q), 125.2 (CH), 113.7 (CH), 113.5 (CH), 61.6 (CH_3), 56.0 (CH_3), 55.2 (CH_3), 52.1 (CH_3). **IR** (ATR): 2936, 2841, 1728, 1480, 1249, 1051, 804, 548 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 302 (100) [M^+], 287 (20), 271 (30), 259 (20), 240 (20), 225 (15), 213 (20). **HR-MS** (EI) *m/z* calcd for $C_{17}H_{18}O_5$ [M^+] 302.1154, found 302.1146.



125ka **125ka'**

The general procedure **A** was followed using benzoic acid **124k** (61 mg, 0.50 mmol), 1-iodo-4-methoxybenzene **14a'** (351 mg, 1.50 mmol, 3.0 equiv) and K_2CO_3 (276 mg, 2.00 mmol, 4.0 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **125ka** (143 mg, 82%) and the diarylated product **125ka'** (19 mg, 16%).

Methyl 4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-carboxylate (125ka):

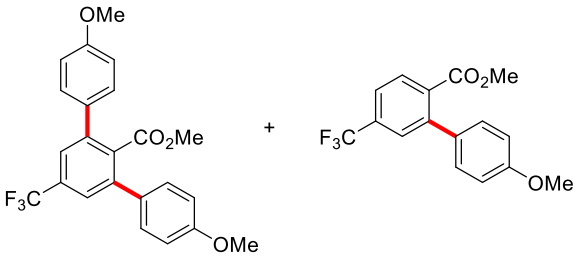
Colorless solid. **M. p.** = 112−113 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.47 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.39–7.30 (m, 6H), 6.95 (d, *J* = 8.9 Hz, 4H), 3.85 (s, 6H), 3.45 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 170.2 (C_q), 159.1 (C_q), 139.8 (C_q), 132.9 (C_q), 132.7 (C_q), 129.5 (CH), 129.2 (CH), 128.5 (CH), 113.7 (CH), 55.2 (CH_3), 51.8 (CH_3). **IR** (ATR): 2920, 2835, 1730, 1586, 1513, 1246, 1103, 1027 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 348 (100) [M^+], 317 (90), 302 (10), 285 (10), 274 (20), 259 (10), 202 (20). **HR-MS** (EI) *m/z* calcd for $C_{22}H_{20}O_4$ [M^+] 348.1362, found 348.1368.

The analytical data are in accordance with those previously reported in the literature.[5]

Methyl 4'-methoxy-[1,1'-biphenyl]-2-carboxylate (125ka'):

Colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.80–7.73 (m, 1H), 7.55–7.43 (m, 1H), 7.38–7.33 (m, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 3.65 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 169.4 (C_q), 158.9 (C_q), 142.0 (C_q), 133.6 (C_q), 131.2 (CH), 130.8 (C_q), 130.7 (CH), 129.7 (CH), 129.4 (CH), 126.8 (CH), 113.5 (CH), 55.2 (CH_3), 51.9 (CH_3). **IR** (ATR): 2949, 2836, 1716, 1610, 1516, 1238, 761 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 242 (95) [M^+], 211 (100), 196 (10), 183 (15), 168 (30), 139 (40). **HR-MS** (EI) *m/z* calcd for $C_{15}H_{14}O_3$ [M^+] 242.0943, found 242.0946.

The analytical data are in accordance with those previously reported in the literature.[111b]



125la **125la'**

The general procedure **A** was followed using benzoic acid **125l** (95 mg, 0.50 mmol), 1-iodo-4-methoxybenzene (**14a'**) (351 mg, 1.50 mmol, 3.0 equiv) and K_2CO_3 (276 mg, 2.00 mmol, 4.0 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 10:1) yielded **125la** (108 mg, 52%) and the diarylated product **125la'** (39 mg, 25%).

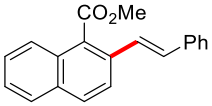
Methyl 4,4''-dimethoxy-5'-(trifluoromethyl)-[1,1':3',1''-terphenyl]-2'-carboxylate (125la):

Colorless solid. **M. p.** = 133−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, J = 0.7 Hz, 2H), 7.33 (d, J = 8.9 Hz, 4H), 6.94 (d, J = 8.9 Hz, 4H), 3.83 (s, 6H), 3.44 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 169.1 (C_q), 159.6 (C_q), 140.8 (C_q), 135.9 (q, $^4J_{C\text{-}F}$ = 1.1 Hz, C_q), 131.3 (q, $^2J_{C\text{-}F}$ = 32.6 Hz, C_q), 131.5 (C_q), 129.5 (CH), 125.1 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, CH), 123.7 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, C_q), 114.0 (CH), 55.3 (CH_3), 52.1 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -62.79 (s). **IR** (ATR): 2943, 2841, 1735, 1609, 1517, 1363, 1120, 809 cm^{-1}. **HR-MS** (ESI) *m/z* calcd for $C_{23}H_{20}F_3O_4$ [M+H$^+$] 417.1308, found 417.1316.

Methyl 4'-methoxy-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylate (125la'):

Colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.85 (dd, J = 8.6, 0.9 Hz, 1H), 7.64–7.57 (m, 2H), 7.24 (d, J = 8.9 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 3.84 (s, 3H), 3.68 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 168.4 (C_q), 159.5 (C_q), 142.5 (C_q), 134.2 (q, $^4J_{C\text{-}F}$ = 1.0 Hz, C_q), 132.8 (q, $^2J_{C\text{-}F}$ = 32.6 Hz, C_q), 132.0 (C_q), 130.1 (CH), 129.4 (CH), 127.4 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, CH), 123.6 (q, $^4J_{C\text{-}F}$ = 272.9 Hz, C_q), 123.5 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, CH), 113.8 (CH), 55.3 (CH_3), 52.3 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -63.00 (s). **IR** (ATR): 2953, 2840, 1724, 1610, 1518, 1244, 1125, 833 cm^{-1}. **HR-MS** (ESI) *m/z* calcd for $C_{16}H_{14}F_3O_3$ [M+H$^+$] 311.0890, found 311.0899.

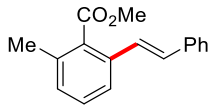
Ruthenium(II)-Catalyzed C–H Alkeynylation



Methyl (*E*)-2-styryl-1-naphthoate (136a): A suspension of [Ru(O_2CMes)$_2$(*p*-cymene)] (**16**) (28.1 mg, 10 mol %), PCy_3 (14.0 mg, 10 mol %), K_2CO_3 (276 mg, 2.00 mmol, 4.0 equiv), benzoic acid **124g** (86 mg, 0.50 mmol) and (*E*)-(2-bromovinyl)benzene (**135**) (275 mg, 1.50 mmol, 3.0 equiv) in NMP (2.0 mL) was stirred under N_2 for 16 h at 120 °C. At ambient temperature, MeCN (3.0 mL), K_2CO_3 (207 mg, 1.50 mmol)

and MeI (355 mg, 2.50 mmol) were added and the mixture was stirred at 50 ºC for another 2 h. At ambient temperature, the mixture was diluted with MTBE (120 mL), then washed with H_2O (20 mL) and brine (20 mL) sequentially. The organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 30:1) to yield the methyl ester **136a** (86 mg, 60%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.90–7.78 (m, 4H), 7.58–7.43 (m, 4H), 7.41–7.17 (m, 5H), 4.09 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 169.9 (C_q), 137.0 (C_q), 132.5 (C_q), 132.5 (C_q), 132.0 (CH), 130.1 (C_q), 130.0 (CH), 129.8 (C_q), 128.7 (CH), 128.1 (CH), 128.1 (CH), 127.4 (CH), 126.8 (CH), 126.3 (CH), 125.4 (CH), 125.1 (CH), 122.6 (CH), 52.5 (CH_3). **IR** (ATR): 3056, 2948, 1719, 1508, 1434, 1213, 1134, 1032 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 288 (80) [M^+], 257 (30), 228 (100), 226 (40), 215 (10), 202 (20). **HR-MS** (ESI) *m/z* calcd for $C_{20}H_{17}O_2$ [M+H^+] 289.1223, found 289.1218.

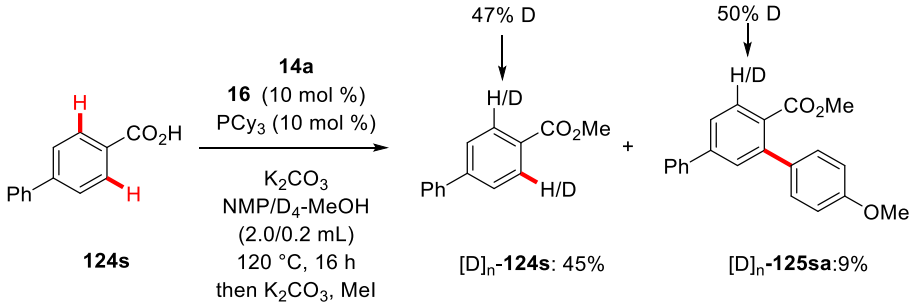


Methyl (*E*)-2-methyl-6-styrylbenzoate (136b): A suspension of [Ru(O_2CMes)$_2$(*p*-cymene)] (**16**) (28.1 mg, 10 mol %), PCy_3 (14.0 mg, 10 mol %), K_2CO_3 (276 mg, 2.00 mmol, 4.0 equiv), benzoic acid **124a** (68 mg, 0.50 mmol) and (*E*)-(2-bromovinyl)benzene (**135**) (275 mg, 1.50 mmol, 3.0 equiv) in NMP (2.0 mL) was stirred under N_2 for 16 h at 120 ºC. At ambient temperature, MeCN (3.0 mL), K_2CO_3 (207 mg, 1.50 mmol) and MeI (355 mg, 2.50 mmol) were added and the mixture was stirred at 50 ºC for another 2 h. At ambient temperature, the mixture was diluted with MTBE (120 mL), then washed with H_2O (20 mL) and brine (20 mL) sequentially. The organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 30:1) to yield the methyl ester **136b** (71 mg, 56%) as a pale yellow oil.

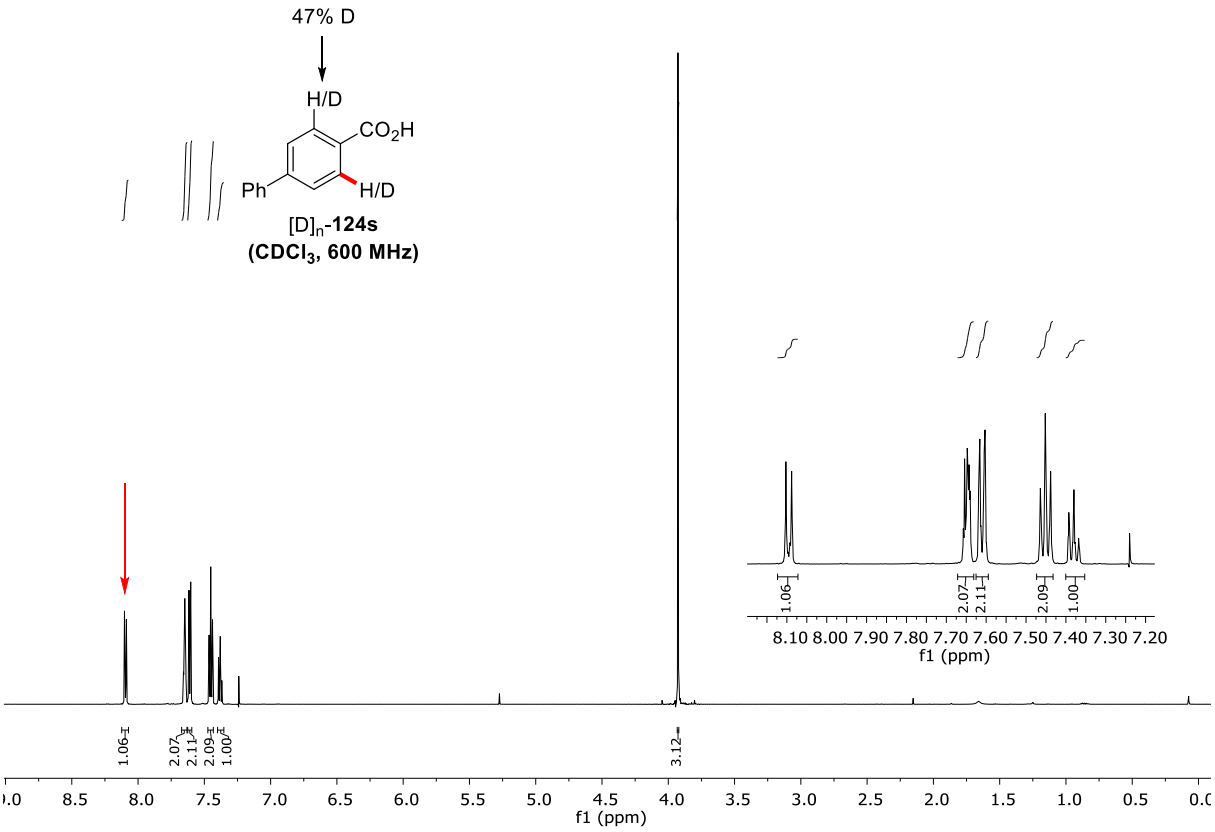
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.57–7.43 (m, 3H), 7.39–7.23 (m, 4H), 7.17–7.00 (m, 3H), 3.95 (s, 3H), 2.34 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 170.2 (C_q), 137.1 (C_q), 135.2 (C_q), 135.0 (C_q), 132.9 (C_q), 131.3 (CH), 129.5 (CH), 129.2 (CH), 128.6 (CH), 127.9 (CH), 126.7 (CH), 125.6 (CH), 123.0 (CH), 52.1 (CH_3), 19.7 (CH_3). **IR** (ATR): 3026, 2949, 2862, 1721, 1588, 1436, 1265, 1068 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 252 (100) [M^+], 237 (10), 220 (50), 193 (30), 178 (50), 165 (20). **HR-MS** (EI) *m/z* calcd for $C_{17}H_{16}O_2$ [M^+] 252.1150, found 252.1148.

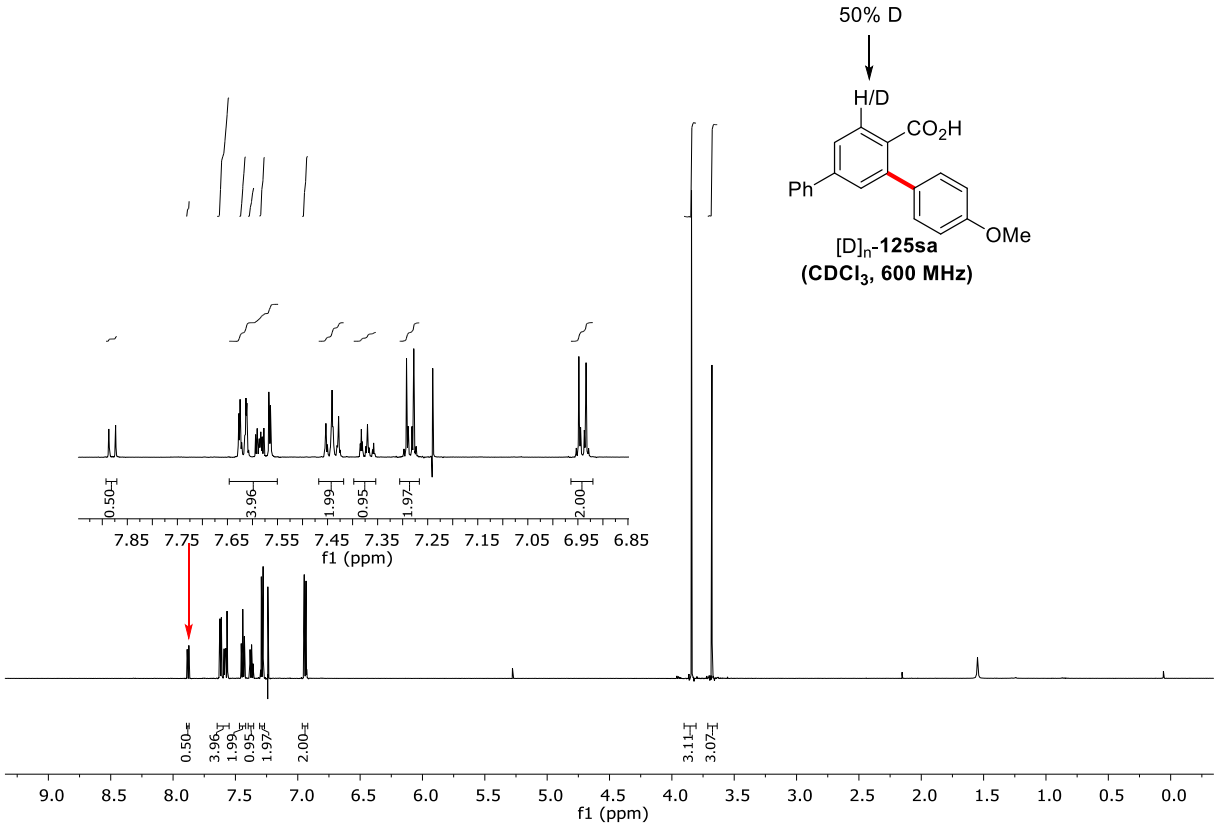
The analytical data are in accordance with those previously reported in the literature.[145]

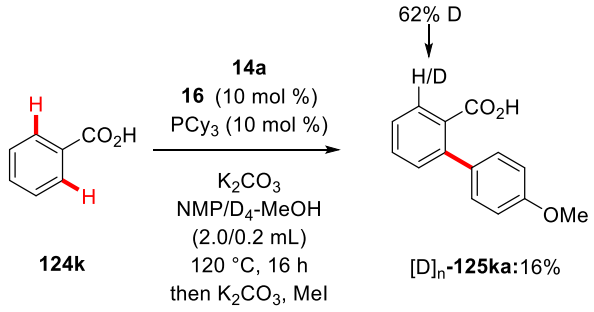
H/D Exchange Experiments



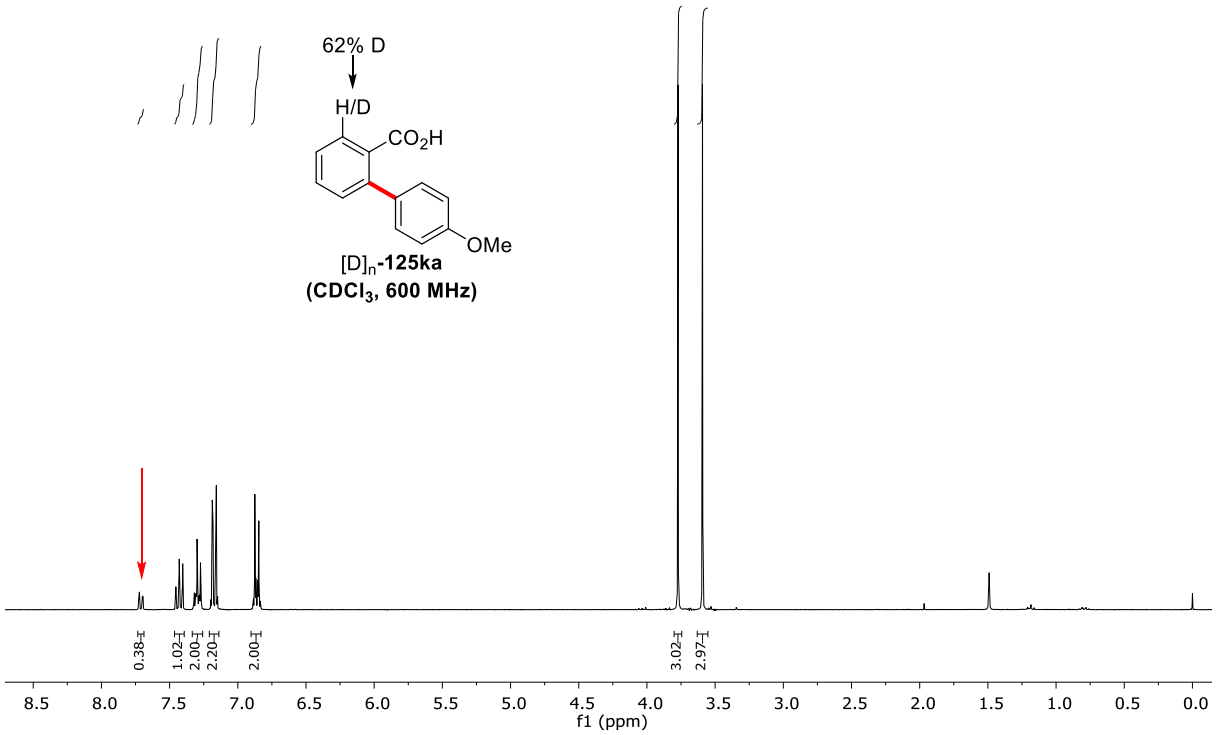
A suspension of 1-bromo-4-methoxybenzene (**14a**) (140 mg, 0.75 mmol), 4-phenylbenzoic acid (**124s**) (99 mg, 0.50 mmol), [Ru(O_2CMes)$_2$(*p*-cymene)] (**16**) (28.1 mg, 10 mol %), PCy_3 (14.0 mg, 10 mol %), K_2CO_3 (138 mg, 1.00 mmol) in a solvent mixture of NMP (2.0 mL) and CD_3OD (0.2 mL) was stirred at 120 ºC for 16 h in a seal tube under a N_2 atmosphere. At ambient temperature, MeCN (3.0 mL), K_2CO_3 (207 mg, 1.50 mmol) and MeI (355 mg, 2.50 mmol) were added and the mixture was stirred at 50 ºC for another 2.0 h. At ambient temperature, the mixture was diluted with MTBE (120 mL), then washed with H_2O (20 mL) and brine (20 mL) sequentially. The organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) to yield [D]$_n$-**124s** (48 mg, 45%) and [D]$_n$-**125sa** (14 mg, 9%). The D-incorporation in [D]$_n$-**124s** and [D]$_n$-**125sa** was estimated by ^{1}H-NMR spectroscopy.





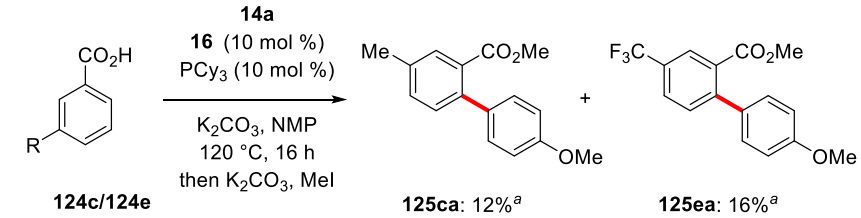


A suspension of 1-bromo-4-methoxybenzene (**14a**) (140 mg, 0.75 mmol), benzoic acid (**124k**) (61 mg, 0.50 mmol), [Ru(MesCO$_2$)$_2$(*p*-cymene)] (**16**) (28.1 mg, 10 mol %), PCy$_3$ (14.0 mg, 10 mol %), K$_2$CO$_3$ (138 mg, 1.00 mmol) in a solvent mixture of NMP (2.0 mL) and CD$_3$OD (0.2 mL) was stirred at 120 ºC for 16 h in a seal tube under a N$_2$ atmosphere. At ambient temperature, MeCN (3.0 mL), K$_2$CO$_3$ (207 mg, 1.50 mmol) and MeI (355 mg, 2.50 mmol) were added and the mixture was stirred at 50 ºC for another 2.0 h. At ambient temperature, the mixture was diluted with MTBE (120 mL), then washed with H$_2$O (20 mL), and brine (20 mL) sequentially. The organic phase was dried over Na$_2$SO$_4$, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to yield [D]$_n$-**125ka** (18 mg, 16%). The D-incorporation in [D]$_n$-**125ka** was estimated by ^{1}H-NMR spectroscopy.

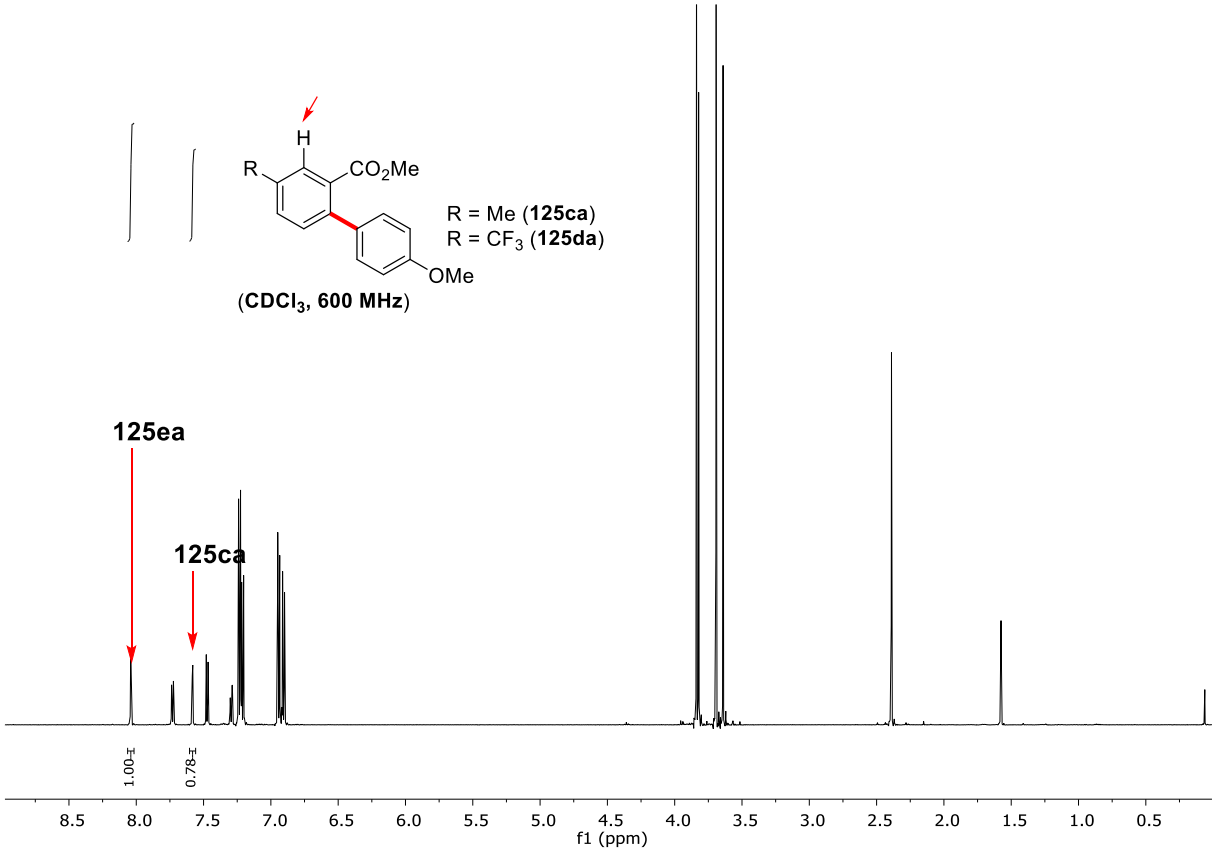


Competition experiments

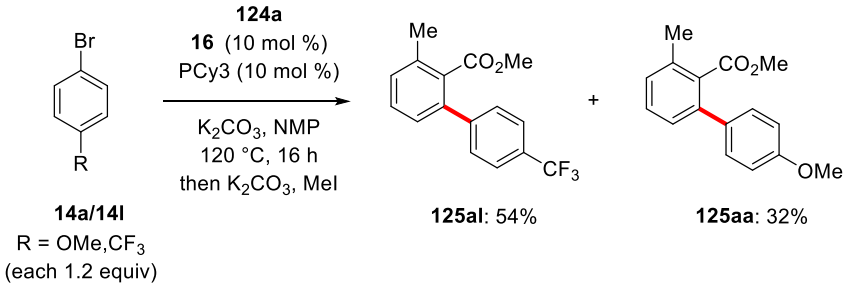
Intermolecular competition experiment between benzoic acids **124c** and **124e**:



A suspension of 1-bromo-4-methoxybenzene (**14a**) (94 mg, 0.50 mmol), 3-methylbenzoic acid (**124c**) (82 mg, 0.60 mmol), 3-(trifluoromethyl)benzoic (**124e**) (114 mg, 0.60 mmol), [$Ru(O_2CMes)_2$(*p*-cymene)] (28.1 mg, 10 mol %), PCy_3 (14.0 mg, 10 mol %), K_2CO_3 (138 mg, 1.00 mmol) in NMP (2.0 mL) was stirred under N_2 for 16 h at 120 ºC. At ambient temperature, MeCN (3.0 mL), K_2CO_3 (207 mg, 1.50 mmol) and MeI (355 mg, 2.50 mmol) were added and the mixture was stirred at 50 ºC for another 2 h. At ambient temperature, the mixture was diluted with MTBE (120 mL), then washed with H_2O (20 mL) and brine (20 mL) sequentially. The organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) to yield the mixture of **125ca** and **125ea** (41 mg). The ratio was calculated based on ^{1}H-NMR analysis.

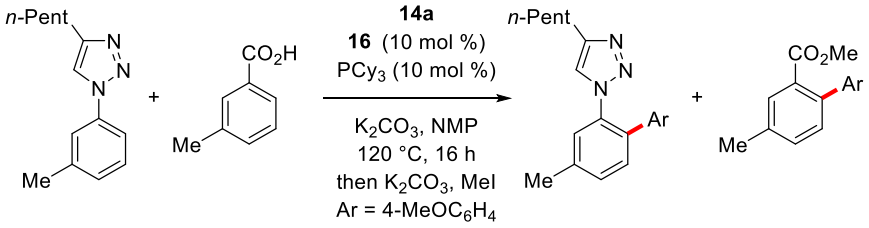


Intermolecular Competition Experiment between aryl bromides **14l** and **14a**:



A suspension of 2-methylbenzoic acid (**124a**) (68 mg, 0.50 mmol), 1-bromo-4-methoxybenzene (**14a**) (112 mg, 0.60 mmol), 1-bromo-4-(trifluoromethyl)benzene (**14l**) (135 mg, 0.60 mmol), [Ru($MesCO_2$)$_2$(*p*-cymene)] (**16**) (28.1 mg, 10 mol %), PCy_3 (14.0 mg, 10 mol %), K_2CO_3 (138 mg, 1.00 mmol) in NMP (2.0 mL) was stirred under N_2 for 16 h at 120 ºC. At ambient temperature, MeCN (3.0 mL), K_2CO_3 (207 mg, 1.50 mmol) and MeI (355 mg, 2.50 mmol) were added and the mixture was stirred at 50 ºC for another 2.0 h. At ambient temperature, the mixture was diluted with MTBE (120 mL), then washed with H_2O (20 mL) and brine (20 mL) sequentially. The organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to yield **125al** (79 mg, 54%) and **125aa** (41 mg, 32%).

Intermolecular Competition Experiment between Benzoic acid **124c** and triazole **13b**:

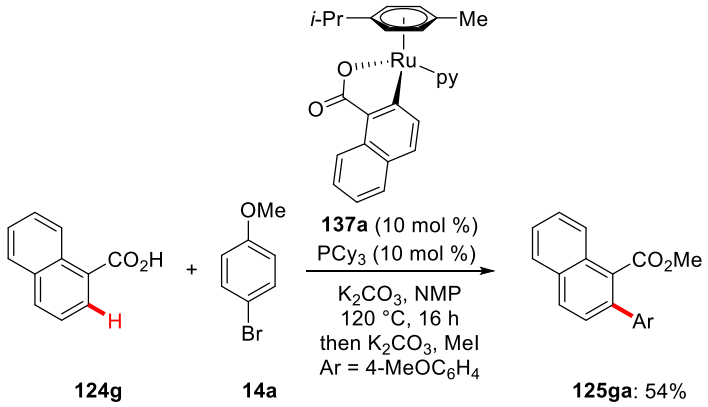


A suspension of 1-bromo-4-methoxybenzene (**14a**) (94 mg, 0.50 mmol), 3-methylbenzoic acid (**124c**) (82 mg, 0.60 mmol), 4-pentyl-1-(*m*-tolyl)-1*H*-1,2,3-triazole (**13b**) (138 mg, 0.60 mmol), [Ru(O_2CMes)$_2$(*p*-cymene)] (**16**) (28.1 mg, 10 mol %), PCy_3 (14.0 mg, 10 mol %), K_2CO_3 (138 mg, 1.00 mmol) in NMP (2.0 mL) was stirred under N_2 for 16 h at 120 ºC. At ambient temperature, MeCN (3.0 mL), K_2CO_3 (207 mg, 1.50 mmol) and MeI (355 mg, 2.50 mmol) were added and the mixture was stirred at 50 ºC for another 2.0 h. At ambient temperature, the mixture was diluted with MTBE (120 mL), then washed with H_2O (20 mL) and brine (20 mL) sequentially. The organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to yield **15b** (Colorless oil, 94 mg, 56%) and **125ca** (5.1 mg, 4%).

1-(4'-Methoxy-4-methyl-[1,1'-biphenyl]-2-yl)-4-pentyl-1*H*-1,2,3-triazole (15b):

^{1}H NMR (300 MHz, $CDCl_3$) δ =7.41 (s, 1H), 7.36–7.28 (m, 2H), 6.95 (d, J = 8.7 Hz, 2H), 6.90 (s, 1H), 6.77 (d, J = 8.7 Hz, 2H), 3.75 (s, 3H), 2.60 (t, J = 7.5 Hz, 2H), 2.42 (s, 3H), 1.53 (p, J = 7.5 Hz, 2H), 1.34–1.10 (m, 4H), 0.84 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 159.0 (C_q), 147.8 (C_q), 138.2 (C_q), 134.9 (C_q), 133.6 (C_q), 130.6 (CH), 130.3 (CH), 129.7 (C_q), 129.5 (CH), 127.0 (CH), 122.9 (CH), 113.9 (CH), 55.1 (CH_3), 31.0 (CH_2), 28.9 (CH_2), 25.2 (CH_2), 22.3 (CH_2), 20.8 (CH_3), 13.8 (CH_3). **IR** (ATR): 2927, 2837, 1609, 1638, 1493, 1464, 1245, 1018 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 335 (10) [M^+], 306 (60), 292 (30), 278 (30), 264 (30), 250 (100), 237 (30). **HR-MS** (EI) *m/z* calcd for $C_{21}H_{25}N_3O$ [M^+] 335.1998, found 335.1991.

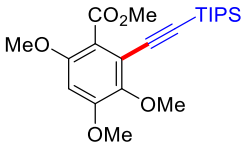
C–H Arylations with Ruthenacycle 137a



124g **14a** **125ga**: 54%

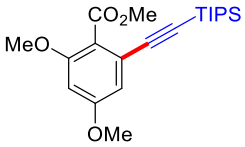
A suspension of 1-naphthoic acid (**124g**) (0.50 mmol, 86 mg), 1-bromo-4-methoxybenzene (**14a**) (140 mg, 0.75 mmol), ruthenacycle **137a** (24.2 mg, 10 mol %), PCy_3 (14.0 mg, 10 mol %), K_2CO_3 (138 mg, 1.00 mmol) in NMP (2.0 mL) was stirred under N_2 for 16 h at 120 ºC. At ambient temperature, MeCN (3.0 mL), K_2CO_3 (207 mg, 1.50 mmol) and MeI (355 mg, 2.50 mmol) were added and the mixture was stirred at 50 ºC for another 2.0 h. At ambient temperature, the mixture was diluted with MTBE (120 mL) then washed with H_2O (20 mL) and brine (20 mL) sequentially. The organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) to yield **125ga** (95 mg, 54%, based on 0.60 mmol) and starting material methyl 1-naphthoate (31 mg, 28%).

5.3.2 Ruthenium(II)-Catalyzed C−H Alkynylation of Weakly Coordinating Benzoic Acids



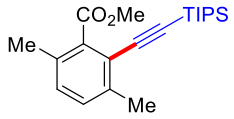
Methyl 3,4,6-trimethoxy-2-[(triisopropylsilyl)ethynyl]benzoate (126ta): A suspension of [Ru(O_2CMes)$_2$(*p*-cymene)] (**16**) (56.2 mg, 10 mol %), K_2CO_3 (276 mg, 2.00 mmol), benzoic acid **124t** (212.2 mg, 1.00 mmol), and alkynyl bromide **33a** (339.7 mg, 1.30 mmol) in 1,4-dioxane (2.0 mL) was stirred under N_2 for 16 h at 120 ºC. At ambient temperature, MeCN (6.0 mL), K_2CO_3 (276 mg, 2.0 mmol) and MeI (710 mg, 5.00 mmol) were added and the mixture was stirred at 50 ºC for additional 2 h. At ambient temperature, the mixture was dry-loaded onto silica gel and purified by column chromatography (*n*-hexane/EtOAc 2/1) to give product **126ta** (349.7 mg, 86%) as a colorless solid. When the reaction was running in 0.50 mmol scale, 88% yield was got.

M. p. = 57−58 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 6.46 (s, 1H), 3.84 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 1.14−1.04 (m, 21H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 166.7 (C_q), 154.3 (C_q), 152.9 (C_q), 144.8 (C_q), 118.5 (C_q), 117.0 (C_q), 99.5 (C_q), 99.1 (C_q), 98.2 (CH), 61.0 (CH_3), 56.6 (CH_3), 56.1 (CH_3), 52.3 (CH_3), 18.5 (CH_3), 11.2 (CH). **IR** (neat): 2942, 2864, 2157, 1734, 1585, 1267, 881, 674 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 429 (10) [M+Na$^+$], 407 (100) [M+H$^+$]. **HR-MS** (ESI) *m/z* calcd for $C_{22}H_{35}O_5Si$ [M+H$^+$] 407.2248, found 407.2247.



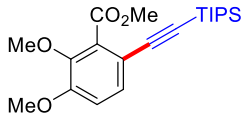
Methyl 2,4-dimethoxy-6-[(triisopropylsilyl)ethynyl]benzoate (126ua): The general procedure **B** was followed using benzoic acid **124u** (91 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **126ua** (143 mg, 76%) as a pale yellow solid.

M. p. = 46−47 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 6.55 (d, *J* = 2.2 Hz, 1H), 6.41 (d, *J* = 2.2 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 1.14−1.04 (m, 21H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 167.0 (C_q), 161.1 (C_q), 157.6 (C_q), 123.0 (C_q), 119.4 (C_q), 108.5 (CH), 103.7 (C_q), 99.6 (CH), 94.4 (C_q), 55.9 (CH_3), 55.5 (CH_3), 52.2 (CH_3), 18.5 (CH_3), 11.2 (CH). **IR** (neat): 2943, 2865, 2150, 1732, 1574, 1267, 1156, 881, 674 cm^{-1}. **MS** (ESI) m/z (relative intensity) 399 (20) [M+Na$^+$], 377 (100) [M+H$^+$]. **HR-MS** (ESI) m/z calcd for $C_{21}H_{33}O_4Si$ [M+H$^+$] 377.2143, found 377.2139.



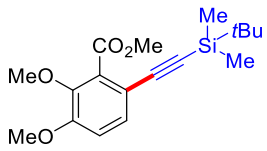
Methyl 3,6-dimethyl-2-[(triisopropylsilyl)ethynyl]benzoate (126va): The general procedure **B** was followed using benzoic acid **124v** (75 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1) and then by HPLC yielded **126va** (129 mg, 75%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.11 (d, *J* = 7.9 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 3.88 (s, 3H), 2.41 (s, 3H), 2.24 (s, 3H), 1.17−1.02 (m, 21H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 169.4 (C_q), 138.5 (C_q), 136.8 (C_q), 131.9 (C_q), 130.2 (CH), 129.8 (CH), 120.4 (C_q), 102.7 (C_q), 98.7 (C_q), 52.2 (CH_3), 20.6 (CH_3), 18.9 (CH_3), 18.6 (CH_3), 11.2 (CH). **IR** (neat): 2943, 2864, 2150, 1734, 1273, 1136, 882, 757, 672 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 367 (10) [M+Na^+], 345 (100) [M+H^+]. **HR-MS** (ESI) *m/z* calcd for $C_{21}H_{33}O_2Si$ [M+H^+] 345.2244, found 345.2246.



Methyl 2,3-dimethoxy-6-[(triisopropylsilyl)ethynyl]benzoate (126ja): The general procedure **B** was followed using benzoic acid **124j** (91 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 10:1) yielded **126ja** (154 mg, 82%) as a colorless solid.

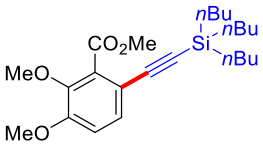
M. p. = 74−75 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.19 (d, *J* = 8.6 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 1.10−1.07 (m, 21H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.6 (C_q), 152.9 (C_q), 145.6 (C_q), 132.0 (C_q), 129.0 (CH), 113.4 (C_q), 113.0 (CH), 103.3 (C_q), 92.5 (C_q), 61.5 (CH_3), 55.9 (CH_3), 52.4 (CH_3), 18.6 (CH_3), 11.3 (CH). **IR** (neat): 2942, 2863, 2149, 1731, 1463, 1272, 1048, 826, 660 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 399 (20) [M+Na^+], 377 (100) [M+H^+]. **HR-MS** (ESI) *m/z* calcd for $C_{21}H_{33}O_4Si$ [M+H^+] 377.2143, found 377.2143.



Methyl 6-[(*tert*-butyldimethylsilyl)ethynyl]-2,3-dimethoxybenzoate (126jb): A suspension of [Ru(O_2CMes)$_2$(*p*-cymene)] (**16**) (28.1 mg, 10 mol %), K_2CO_3 (69 mg, 0.50 mmol), benzoic acid **124j** (91 mg, 0.50 mmol) and (bromoethynyl)(tert-butyl)dimethylsilane (**33b**) (219 mg, 1.00 mmol, 2.0 equiv) in 1,4-dioxane (1.0 mL) was stirred under N_2 for 8 h at 110 ºC. At ambient temperature, MeCN (3.0 mL), K_2CO_3

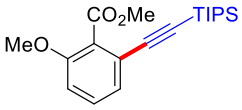
(138 mg, 1.0 mmol) and MeI (355 mg, 2.50 mmol) were added and the mixture was stirred at 50 ºC for additional 2 h. At ambient temperature, the mixture was dry loaded onto silica gel and purified by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **126jb** (112 mg, 67%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.21 (d, *J* = 8.5 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 0.96 (s, 9H), 0.15 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 166.8 (C_q), 153.2 (C_q), 145.8 (C_q), 132.2 (C_q), 129.0 (CH), 113.3 (C_q), 113.1 (CH), 102.1 (C_q), 94.6 (C_q), 61.6 (CH_3), 55.9 (CH_3), 52.4 (CH_3), 26.1 (CH_3), 16.6 (C_q), -4.6 (CH_3). **IR** (neat): 2951, 2931, 2152, 1735, 1486, 1274, 1046, 810, 774 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 357 (70) [M+Na$^+$], 335 (100) [M+H$^+$]. **HR-MS** (ESI) *m/z* calcd for $C_{18}H_{27}O_4Si$ [M+H$^+$] 335.1673, found 335.1675.



Methyl 2,3-dimethoxy-6-((tributylsilyl)ethynyl)benzoate (126jc): The general procedure **B** was followed using benzoic acid **124j** (91 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33c**) (197 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 10:1) yielded **126jc** (54 mg, 26%) as a colorless oil.

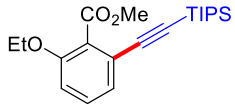
^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.45 (s, 1H), 3.84 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 1.51–1.25 (m, 12H), 0.93–0.82 (m, 9H), 0.70–0.56 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 166.6 (C_q), 154.3 (C_q), 153.0 (C_q), 144.7 (C_q), 118.5 (C_q), 117.0 (C_q), 101.3 (C_q), 98.4 (C_q), 98.2 (CH), 60.9 (CH_3), 56.6 (CH_3), 56.2 (CH_3), 52.2 (CH_3), 26.4 (CH_2), 26.1 (CH_2), 13.7 (CH_3), 12.9 (CH_2). **IR** (neat): 2955, 2919, 2855, 2157, 1722, 1586, 1428, 1268, 1208 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 448 (30) [M$^+$], 433 (10), 417 (10), 391 (100), 377 (30). **HR-MS** (EI) *m/z* calcd for $C_{25}H_{40}O_5Si$ [M+H$^+$] 448.2645, found 448.2649.



Methyl 2-methoxy-6-[(triisopropylsilyl)ethynyl]benzoate (126ba): The general procedure **B** was followed using benzoic acid **124b** (76 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1) and then HPLC yielded **126ba** (135 mg, 78%) as a colorless oil.

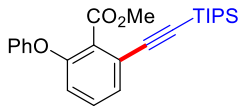
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.27 (dd, *J* = 8.5, 7.8, 1H), 7.09 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.87 (dd, *J* = 8.5, 1.0 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 1.14–1.08 (m, 21H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 167.1 (C_q), 156.0 (C_q), 130.2 (CH), 126.4 (C_q), 124.9 (CH), 122.1 (C_q), 111.4 (CH), 103.4 (C_q), 94.7 (C_q), 56.0 (CH_3), 52.4 (CH_3), 18.5 (CH_3), 11.2 (CH). **IR** (neat): 2942, 2865, 2152, 1737, 1465, 1261, 1066, 882, 667 cm^{-1}. **MS** (ESI)

m/z (relative intensity) 369 (20) [M+Na$^+$], 347 (100) [M+H$^+$]. **HR-MS** (ESI) m/z calcd for $C_{20}H_{31}O_3Si$ [M+H$^+$] 347.2037, found 347.2033.



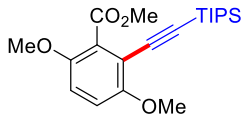
Methyl 2-ethoxy-6-[(triisopropylsilyl)ethynyl]benzoate (126wa): The general procedure **B** was followed using benzoic acid **124w** (83 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **126wa** (137 mg, 76%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.22 (dd, J = 8.4, 7.8 Hz, 1H), 7.06 (dd, J = 7.8, 0.9 Hz, 1H), 6.84 (dd, J = 8.4, 0.9 Hz, 1H), 4.02 (q, J = 7.0 Hz, 2H), 3.87 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H), 1.15–1.02 (m, 21H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 167.2 (C_q), 155.4 (C_q), 130.1 (CH), 126.9 (C_q), 124.8 (CH), 122.0 (C_q), 112.7 (CH), 103.5 (C_q), 94.5 (C_q), 64.6 (CH_2), 52.3 (CH_3), 18.5 (CH_3), 14.6 (CH_3), 11.2 (CH). **IR** (neat): 2943, 2865, 2156, 1738, 1458, 1260, 1065, 669 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 360 (20) [M$^+$], 345 (15), 329 (100). **HR-MS** (EI) *m/z* calcd for $C_{21}H_{32}O_3Si$ [M$^+$] 360.2121, found 360.2111.



Methyl 2-phenoxy-6-[(triisopropylsilyl)ethynyl]benzoate (126xa): The general procedure **B** was followed using benzoic acid **124x** (107 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 40:1) and then HPLC yielded **126xa** (179 mg, 79%) as a pale yellow solid.

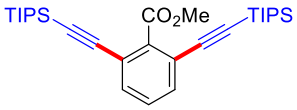
M. p. = 63−64 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.38–7.24 (m, 2H), 7.28–7.17 (m, 2H), 7.16–7.03 (m, 1H), 7.06–6.95 (m, 2H), 6.83 (dd, J = 7.0, 2.4 Hz, 1H), 3.83 (s, 3H), 1.18−1.07 (m, 21H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.3 (C_q), 156.6 (C_q), 153.9 (C_q), 130.2 (CH), 129.6 (CH), 128.8 (C_q), 127.6 (CH), 123.7 (CH), 122.7 (C_q), 119.0 (CH), 118.9 (CH), 103.1 (C_q), 95.4 (C_q), 52.4 (CH_3), 18.6 (CH_3), 11.3 (CH). **IR** (neat): 2943, 2865, 2157, 1735, 1453, 1234, 996, 754, 652 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 408 (20) [M$^+$], 393 (20), 379 (10), 377 (100). **HR-MS** (EI) *m/z* calcd for $C_{25}H_{32}O_3Si$ [M$^+$] 408.2121, found 408.2138.



Methyl 3,6-dimethoxy-2-[(triisopropylsilyl)ethynyl]benzoate (126ya): The general procedure **B** was followed using benzoic acid **124y** (91 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg,

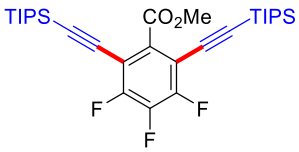
0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1) yielded **126ya** (173 mg, 92%) as a pale yellow solid.

M. p. = 93−94 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.78 (s, 2H), 3.86 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H), 1.10–1.11 (m, 21H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.8 (C_q), 155.0 (C_q), 149.7 (C_q), 127.7 (C_q), 113.1 (CH), 112.6 (CH), 111.8 (C_q), 99.4 (C_q), 99.4 (C_q), 56.7 (CH_3), 56.5 (CH_3), 52.3 (CH_3), 18.5 (CH_3), 11.2 (CH). **IR** (neat): 2942, 2864, 2157, 1732, 1483, 1254, 1055, 673 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 399 (20) [M+Na^+], 377 (100) [M+H^+]. **HR-MS** (ESI) *m/z* calcd for $C_{21}H_{33}O_4Si$ [M+H^+] 377.2143, found 377.2142.



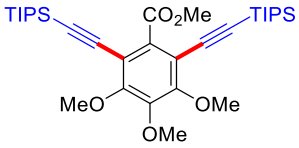
Methyl 2,6-bis[(triisopropylsilyl)ethynyl]benzoate (126ka): The general procedure **B** was followed using benzoic acid **124k** (61 mg, 0.50 mmol) (bromoethynyl)triisopropylsilane (**33a**) (326 mg, 1.25 mmol, 2.50 equiv) and K_2CO_3 (207 mg, 1.50 mmol, 3.0 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 30:1) and then by HPLC yielded **126ka** (144 mg, 58%) as a pale yellow solid.

M. p. = 54−55 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.42 (d, *J* = 7.7 Hz, 2H), 7.25 (t, *J* = 7.7 Hz, 1H), 3.88 (s, 3H), 1.13−1.04 (m, 42H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 167.7 (C_q), 139.5 (C_q), 132.3 (CH), 128.9 (CH), 121.2 (C_q), 103.0 (C_q), 95.4 (C_q), 52.5 (CH_3), 18.5 (CH_3), 11.2 (CH). **IR** (neat): 2942, 2863, 2155, 1737, 1458, 1268, 1113, 882, 669 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 497 (5) [M+H^+], 496 (10) [M^+], 481 (30), 465 (100), 463 (10). **HR-MS** (ESI) *m/z* calcd for $C_{30}H_{49}O_2Si_2$ [M+H^+] 497.3266, found 497.3269.



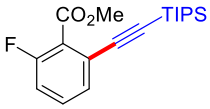
Methyl 3,4,5-trifluoro-2,6-bis[(triisopropylsilyl)ethynyl]benzoate (126za): The general procedure **B** was followed using benzoic acid **124z** (88 mg, 0.50 mmol), (bromoethynyl)triisopropylsilane (**33a**) (326 mg, 1.25 mmol, 2.50 equiv) and K_2CO_3 (207 mg, 1.50 mmol, 3.0 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 25:1) yielded **126za** (231 mg, 84%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.87 (s, 3H), 1.13–1.06 (m, 42H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 165.0 (t, $^{4,4}J_{C\text{-}F}$ = 2.6 Hz, C_q), 151.8 (ddd, $^{1,2,3}J_{C\text{-}F}$ = 259.7, 11.0, 3.7 Hz, C_q), 140.7 (dt, $^{1,2,2}J_{C\text{-}F}$ = 255.8, 15.4 Hz, C_q), 135.7 (d, $^{3}J_{C\text{-}F}$ = 3.5, C_q), 108.2 (dd, $^{2,3}J_{C\text{-}F}$ = 12.8, 7.2 Hz, C_q), 103.3 (t, $^{3,3}J_{C\text{-}F}$ = 3.3, C_q), 94.0 (d, $^{4}J_{C\text{-}F}$ = 3.4, C_q), 53.0 (CH_3), 18.5 (CH_3), 11.1 (CH). **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -126.6 (d, *J* = 21.0 Hz), -156.3 (t, *J* = 21.0 Hz). **IR** (neat): 2944, 2866, 2141, 1749, 1460, 1218, 964, 882, 662 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 573 (100) [M+Na^+], 551 (50) [M+H^+]. **HR-MS** (ESI) *m/z* calcd for $C_{30}H_{45}F_3O_2Si_2Na$ [M+Na^+] 573.2802, found 573.2794.



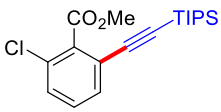
Methyl 3,4,5-trimethoxy-2,6-bis[(triisopropylsilyl)ethynyl]benzoate (126aaa): The general procedure **B** was followed using benzoic acid **124aa** (106 mg, 0.50 mmol) (bromoethynyl)triisopropylsilane (**33a**) (326 mg, 1.25 mmol, 2.50 equiv) and K_2CO_3 (207 mg, 1.50 mmol, 3.0 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **126aaa** (266 mg, 91%) as a pale yellow solid.

M. p. = 70−72 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 3.93 (s, 6H), 3.86 (s, 3H), 3.85 (s, 3H), 1.19–1.07 (m, 42H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.9 (C_q), 155.8 (C_q), 147.1 (C_q), 136.7 (C_q), 111.7 (C_q), 99.0 (C_q), 98.6 (C_q), 61.4 (CH_3), 61.4 (CH_3), 52.6 (CH_3), 18.7 (CH_3), 11.4 (CH). **IR** (neat): 2939, 2863, 2157, 1739, 1460, 1348, 1025, 660 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 609 (40) [M+Na$^+$], 587 (100) [M+H$^+$]. **HR-MS** (ESI) *m/z* calcd for $C_{33}H_{55}O_5Si_2$ [M+H$^+$] 587.3583, found 587.3581.



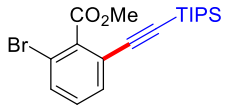
Methyl 2-fluoro-6-[(triisopropylsilyl)ethynyl]benzoate (126aba): The general procedure **B** was followed using benzoic acid **124ab** (70 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) and then by HPLC yielded **126aba** (127 mg, 76%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36–7.25 (m, 2H), 7.11–6.99 (m, 1H), 3.90 (s, 3H), 1.13−1.09 (m, 21H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 164.7 (C_q), 159.3 (d, $^1J_{C\text{-}F}$ = 252.0 Hz, C_q), 131.1 (d, $^3J_{C\text{-}F}$ = 9.1 Hz, CH), 129.0 (d, $^4J_{C\text{-}F}$ = 3.4 Hz, CH), 124.3 (d, $^2J_{C\text{-}F}$ = 17.5 Hz, C_q), 123.6 (d, $^3J_{C\text{-}F}$ = 4.3 Hz, C_q), 116.1 (d, $^2J_{C\text{-}F}$ = 21.6 Hz, CH), 102.6 (d, $^4J_{C\text{-}F}$ = 3.9 Hz, C_q), 96.5 (C_q), 52.7 (CH_3), 18.6 (CH_3), 11.2 (CH). **^{19}F NMR** (283 MHz, $CDCl_3$) δ = -(114.2–114.3) (m). **IR** (neat): 2944, 2865, 2156, 1740, 1460, 1276, 997, 882, 667 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 357 (50) [M+Na$^+$], 335 (100) [M+H$^+$]. **HR-MS** (ESI) *m/z* calcd for $C_{19}H_{28}O_2FSi$ [M+H$^+$] 335.1837, found 335.1840.



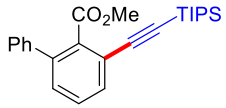
Methyl 2-chloro-6-[(triisopropylsilyl)ethynyl]benzoate (126na): The general procedure **B** was followed using benzoic acid **124n** (78 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1) and then by HPLC yielded **126na** (128 mg, 73%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.39 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.32 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 3.91 (s, 3H), 1.12−1.08 (m, 21H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 166.4 (C_q), 136.3 (C_q), 130.9 (CH), 130.7 (C_q), 130.0 (CH), 129.3 (CH), 122.7 (C_q), 102.4 (C_q), 96.3 (C_q), 52.7 (CH_3), 18.5 (CH_3), 11.2 (CH). **IR** (neat): 2944, 2866, 2169, 1744, 1444, 1270, 1109, 902, 670 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 349 (10) [M–H$^+$], 343 (5), 335 (5), 319 (100). **HR-MS** (ESI) *m/z* calcd for $C_{19}H_{28}ClO_2Si$ [M+H$^+$] 351.1542, found 351.1540.



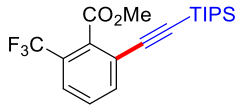
Methyl 2-bromo-6-[(triisopropylsilyl)ethynyl]benzoate (126aca): The general procedure **B** was followed using benzoic acid **124ac** (100 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 40:1) and then by HPLC yielded **126aca** (102 mg, 52%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.51 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.45 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.19 (dd, *J* = 8.1, 7.8 Hz, 1H), 3.93 (s, 3H), 1.14−1.08 (m, 21H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 167.0 (C_q), 138.6 (C_q), 132.4 (CH), 131.4 (CH), 130.1 (CH), 122.8 (C_q), 118.8 (C_q), 102.5 (C_q), 96.4 (C_q), 52.7 (CH_3), 18.5 (CH_3), 11.2 (CH). **IR** (neat): 2943, 2865, 2164, 1741, 1462, 1268, 1104, 878, 666 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 353 (100) [M-41], 413 (25), 403 (25), 395 (20). **HR-MS** (ESI) *m/z* calcd for $C_{19}H_{27}{}^{79}BrO_2SiNa$ [M+Na$^+$] 417.0856, found 417.0850.



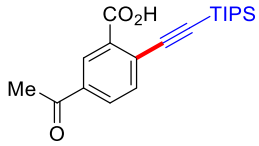
Methyl 3-[(triisopropylsilyl)ethynyl]-[1,1'-biphenyl]-2-carboxylate (126ada): The general procedure **B** was followed using benzoic acid **126ad** (99 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 25:1) and then by HPLC yielded **126ada** (126 mg, 64%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.42–7.28 (m, 7H), 3.63 (s, 3H), 1.16–1.10 (m, 21H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 168.7 (C_q), 139.9 (C_q), 139.7 (C_q), 136.2 (C_q), 131.6 (CH), 129.6 (CH), 129.2 (CH), 128.3 (CH), 128.2 (CH), 127.7 (CH), 121.4 (C_q), 103.7 (C_q), 94.9 (C_q), 52.1 (CH_3), 18.6 (CH_3), 11.2 (CH). **IR** (neat): 2943, 2864, 2157, 1736, 1457, 1260, 896, 744, 667 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 415 (10) [M+Na$^+$], 393 (100) [M+H$^+$]. **HR-MS** (ESI) *m/z* calcd for $C_{25}H_{33}O_2Si$ [M+H$^+$] 393.2244, found 393.2245.



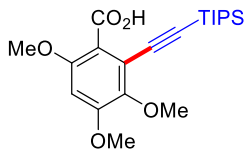
Methyl 2-(trifluoromethyl)-6-[(triisopropylsilyl)ethynyl]benzoate (126aea): The general procedure **B** was followed using benzoic acid **124ae** (95 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 30:1) and then by HPLC yielded **126aea** (133 mg, 69%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.69 (ddd, J = 7.8, 1.3, 0.6 Hz, 1H), 7.61 (ddd, J = 8.0, 1.3, 0.6 Hz, 1H), 7.50–7.43 (m, 1H), 3.93 (s, 3H), 1.13–1.11 (m, 21H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.7 (C_q), 136.0 (q, $^{4}J_{C\text{-}F}$ = 1.1 Hz, CH), 134.9 (q, $^{3}J_{C\text{-}F}$ = 2.3 Hz, C_q), 129.3 (CH), 127.6 (q, $^{2}J_{C\text{-}F}$ = 32.5 Hz, C_q), 125.6 (q, $^{3}J_{C\text{-}F}$ = 4.6 Hz, CH), 123.0 (q, $^{1}J_{C\text{-}F}$ = 273.8 Hz, C_q), 122.6 (C_q), 102.1 (C_q), 97.1 (C_q), 52.9 (CH_3), 18.5 (CH_3), 11.2 (CH). **^{19}F NMR** (282 MHz, $CDCl_3$) δ = -60.47 (s). **IR** (neat): 2945, 2866, 2157, 1745, 1457, 1321, 1132, 909, 666 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 385 (5) [M+H$^+$], 365 (60), 353 (100). **HR-MS** (ESI) *m/z* calcd for $C_{20}H_{27}F_3O_2SiNa$ [M+Na$^+$] 407.1625, found 407.1619.



Methyl 5-acetyl-2-[(triisopropylsilyl)ethynyl]benzoate (126da): The general procedure **B** was followed using benzoic acid **124d** (82 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 30:1) and then by HPLC yielded **126da** (72 mg, 40%) as a pale yellow solid.

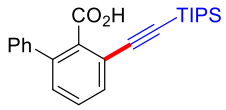
M. p. = 45−46 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.43 (d, J = 1.9 Hz, 1H), 8.00 (dd, J = 8.2, 1.9 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H), 3.93 (s, 3H), 2.62 (s, 3H), 1.16−1.10 (m, 21H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 196.4 (C_q), 166.3 (C_q), 135.9 (C_q), 135.2 (CH), 132.8 (C_q), 130.4 (CH), 130.3 (CH), 127.8 (C_q), 104.4 (C_q), 101.0 (C_q), 52.4 (CH_3), 26.6 (CH_3), 18.6 (CH_3), 11.3 (CH). **IR** (neat): 2942, 2864, 2157, 1725, 1684, 1236, 1072, 880, 605 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 381 (100) [M+Na$^+$], 359 (60) [M+H$^+$]. **HR-MS** (ESI) *m/z* calcd for $C_{21}H_{31}O_3Si$ [M+H$^+$] 359.2037, found 359.2046.



3,4,6-Trimethoxy-2-[(triisopropylsilyl)ethynyl]benzoic acid (126aa´): The general procedure **C** was followed using benzoic acid **124a** (106 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg,

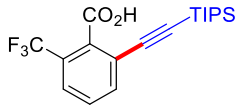
0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc/AcOH 4:1:0.02) yielded **126aa´** (161 mg, 82%) as a colorless solid.

M. p. = 177−178 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.48 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 1.12−1.11 (m, 21H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 169.6 (C_q), 155.2 (C_q), 153.8 (C_q), 145.5 (C_q), 118.3 (C_q), 116.5 (C_q), 101.5 (C_q), 98.9 (C_q), 97.9 (CH), 60.9 (CH_3), 56.8 (CH_3), 56.2 (CH_3), 18.6 (CH_3), 11.3 (CH). **IR** (neat): 2942, 2864, 2163, 1699, 1583, 1209, 1096, 691 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 415 (30) [M+Na^+], 393 (100) [M+H^+]. **HR-MS** (ESI) *m/z* calcd for $C_{21}H_{33}O_5Si$ [M+H^+] 393.2092, found 393.2092.



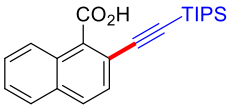
3-[(Triisopropylsilyl)ethynyl]-[1,1'-biphenyl]-2-carboxylic acid (126ada´): The general procedure **C** was followed using benzoic acid **124ad** (99 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc/AcOH 10:1:0.02) yielded **126ada´** (168 mg, 89%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.40 (s_{br}, 1H), 7.58 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.47–7.32 (m, 7H), 1.19−1.12 (m, 21H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 173.4 (C_q), 140.9 (C_q), 139.9 (C_q), 134.2 (C_q), 132.3 (CH), 130.1 (CH), 129.8 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 122.1 (C_q), 103.7 (C_q), 96.0 (C_q), 18.7 (CH_3), 11.3 (CH). **IR** (neat): 2942, 2864, 2159, 1693, 1437, 1288, 1275, 880, 665 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 401 (100) [M+Na^+], 379 (90) [M+H^+]. **HR-MS** (ESI) *m/z* calcd for $C_{24}H_{30}O_2SiNa$ [M+Na^+] 401.1907, found 401.1902.



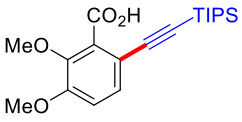
2-(Trifluoromethyl)-6-[(triisopropylsilyl)ethynyl]benzoic acid (126aea´): The general procedure **C** was followed using benzoic acid **124ae** (95 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc/AcOH 15:1:0.02) yielded **126aea´** (175 mg, 95%) as a pale yellow solid.

M. p. = 116−117 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 10.46 (s, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.46−7.43 (m, 1H), 1.10−0.95 (m, 21H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 171.8 (C_q), 136.3 (CH), 133.6 (q, $^{4}J_{C\text{-}F}$ = 2.1 Hz, C_q), 129.7 (CH), 127.9 (q, $^{2}J_{C\text{-}F}$ = 32.7 Hz, C_q), 125.7 (q, $^{3}J_{C\text{-}F}$ = 4.6 Hz, CH), 123.0 (q, $^{1}J_{C\text{-}F}$ = 273.8 Hz, C_q), 122.8 (C_q), 101.8 (C_q), 98.2 (C_q), 18.5 (CH_3), 11.2 (CH). **^{19}F NMR** (282 MHz, $CDCl_3$) δ = -59.8 (s). **IR** (neat): 2943, 2866, 2160, 1712, 1462, 1323, 1131, 665 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 393 (100) [M+Na^+], 371 (10) [M+H^+]. **HR-MS** (ESI) *m/z* calcd for $C_{19}H_{25}F_3O_2SiNa$ [M+Na^+] 393.1468, found 393.1466.



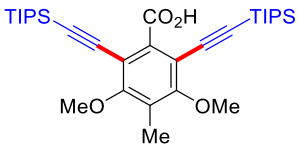
2-[(Triisopropylsilyl)ethynyl]-1-naphthoic acid (126ga´): The general procedure **C** was followed using benzoic acid **124g** (86 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc/AcOH 10:1:0.02) yielded **126ga´** (100 mg, 57%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.13 (ddd, J = 8.5, 1.8, 0.8 Hz, 1H), 7.90–7.85 (m, 2H), 7.66–7.49 (m, 3H), 1.21–1.17 (m, 21H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 174.0 (C_q), 133.1 (C_q), 132.7 (C_q), 130.3 (CH), 129.4 (C_q), 129.0 (CH), 128.2 (CH), 127.8 (CH), 127.1 (CH), 125.2 (CH), 119.9 (C_q), 104.4 (C_q), 97.4 (C_q), 18.7 (CH_3), 11.4 (CH). **IR** (neat): 2942, 2864, 2128, 1697, 1462, 1256, 820, 744, 648 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 352 (5) [M^+], 309 (100), 267 (10), 249 (10), 239 (30), 179 (10), 151 (10). **HR-MS** (EI) *m/z* calcd for $C_{22}H_{28}O_2Si$ [M^+] 352.1859, found 352.1866.



2,3-Dimethoxy-6-[(triisopropylsilyl)ethynyl]benzoic acid (126ja´): The general procedure **C** was followed using benzoic acid **124j** (91 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc/AcOH 4:1:0.02) yielded **126ja´** (173 mg, 96%) as a colorless solid.

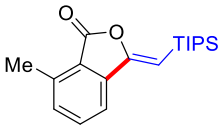
M. p. = 113−115 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.25 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 1.14−1.08 (m, 21H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 171.4 (C_q), 153.1 (C_q), 146.2 (C_q), 130.5 (C_q), 129.5 (CH), 114.0 (C_q), 113.6 (CH), 103.1 (C_q), 93.7 (C_q), 61.7 (CH_3), 56.0 (CH_3), 18.6 (CH_3), 11.2 (CH). **IR** (neat): 2941, 2890, 2154, 1703, 1459, 1274, 1045, 812, 676 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 385 [M+Na^+] (50), 363 (100) [M+H^+]. **HR-MS** (ESI) *m/z* calcd for $C_{20}H_{31}O_4Si$ [M+H^+] 363.1986, found 363.1985.



3,5-Dimethoxy-4-methyl-2,6-bis[(triisopropylsilyl)ethynyl]benzoic acid (126aaa´): The general procedure **C** was followed using benzoic acid **124aa** (98 mg, 0.50 mmol) (bromoethynyl)triisopropylsilane (**33a**) (326 mg, 1.25 mmol, 2.50 equiv) and K_2CO_3 (207 mg, 1.50 mmol, 3.0 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc/AcOH 10:1:0.02) yielded **126aaa´** (197 mg, 71%) as a pale yellow solid.

M. p. = 198−199 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 3.94 (s, 6H), 2.23 (s, 3H), 1.17−1.10 (m, 42H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 170.5 (C_q), 161.1 (C_q), 137.6 (C_q), 127.9 (C_q), 112.1 (C_q), 100.2 (C_q), 99.0 (C_q), 60.7 (CH_3), 18.6 (CH_3), 11.3 (CH), 9.6 (CH_3). **IR** (neat): 2942, 2865, 2153, 1703, 1450, 1389, 994, 882, 661 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 557 (3) [M+H$^+$], 556 (5) [M$^+$], 537 (10), 515 (15), 514 (40), 513 (100), 455 (5). **HR-MS** (EI) *m/z* calcd for $C_{32}H_{52}O_4Si_2$ [M$^+$] 556.3404, found 556.3420.

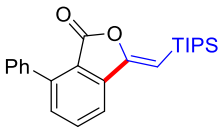
C–H Alkynylation/Cyclization Cascade



(*Z*)-7-Methyl-3-[(triisopropylsilyl)methylene]isobenzofuran-1(3*H*)-one (140a): A suspension of [$RuCl_2$(*p*-cymene)] (15.3 mg, 5.0 mol %), X-phos (23.8 mg, 10 mol %), K_2CO_3 (138 mg, 1.00 mmol), benzoic acid **124a** (68 mg, 0.50 mmol), and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv) in NMP (2.0 mL) was stirred under N_2 for 16 h at 120 °C. At ambient temperature, the mixture was diluted with MTBE (120 mL), then sequentially washed with H_2O (20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) to yield **140a** (125 mg, 79%) as a colorless solid.

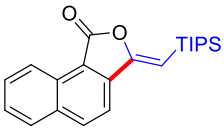
M. p. = 135−136 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.61–7.49 (m, 2H), 7.36–7.27 (m, 1H), 5.53 (s, 1H), 2.69 (s, 3H), 1.41–1.29 (m, 3H), 1.11 (d, *J* = 7.2 Hz, 18H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 167.6 (C_q), 156.5 (C_q), 139.7 (C_q), 139.1 (C_q), 133.9 (CH), 131.7 (CH), 122.6 (C_q), 118.2 (CH), 99.7 (CH), 18.8 (CH_3), 17.5 (CH_3) 11.7 (CH). **IR** (ATR): 2940, 2863, 1762, 1637, 1461, 1255, 974 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 339 (90) [M+Na$^+$], 317 (100) [M+H$^+$]. **HR-MS** (ESI) *m/z* calcd for $C_{19}H_{29}O_2Si$ [M+H$^+$] 317.1931, found 317.1935.

The analytical data are in accordance with those previously reported in the literature.[146]



(*Z*)-7-Phenyl-3-[(triisopropylsilyl)methylene]isobenzofuran-1(3*H*)-one (140b): A suspension of [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %), X-phos (23.8 mg, 10 mol %), K_2CO_3 (138 mg, 1.00 mmol), benzoic acid **124ad** (99 mg, 0.50 mmol), and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv) in NMP (2.0 mL) was stirred under N_2 for 16 h at 120 °C. At ambient temperature, the mixture was diluted with MTBE (120 mL), then sequentially washed with H_2O (20 mL) and brine (20 mL). The

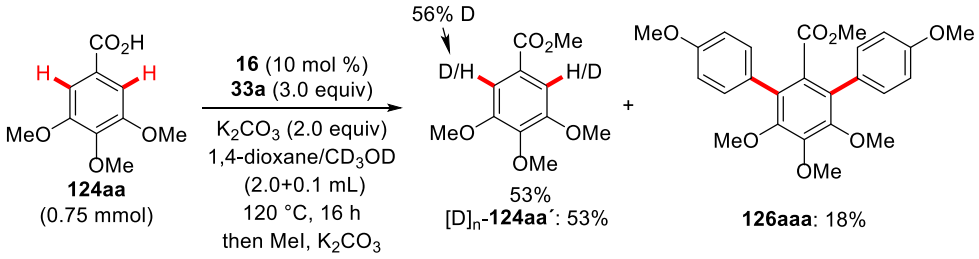
organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) to yield **140b** (91 mg, 48%) as a colorless solid.
M. p. = 96−97 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.77–7.68 (m, 2H), 7.60–7.53 (m, 2H), 7.52–7.39 (m, 4H), 5.61 (s, 1H), 1.42–1.31 (m, 3H), 1.12 (d, *J* = 7.4 Hz, 18H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.2 (C_q), 156.1 (C_q), 142.2 (C_q), 140.4 (C_q), 136.2 (C_q), 134.0 (CH), 131.8 (CH), 129.4 (CH), 128.5 (CH), 128.0 (CH), 120.8 (C_q), 119.6 (CH), 99.8 (CH), 18.8 (CH_3), 11.6 (CH). **IR** (ATR): 2938, 2862, 1772, 1638, 1473, 1238, 976, 879 cm^{-1}. **HR-MS** (ESI) *m/z* calcd for $C_{24}H_{31}O_2Si$ [M+H$^+$] 379.2088, found 379.2091.



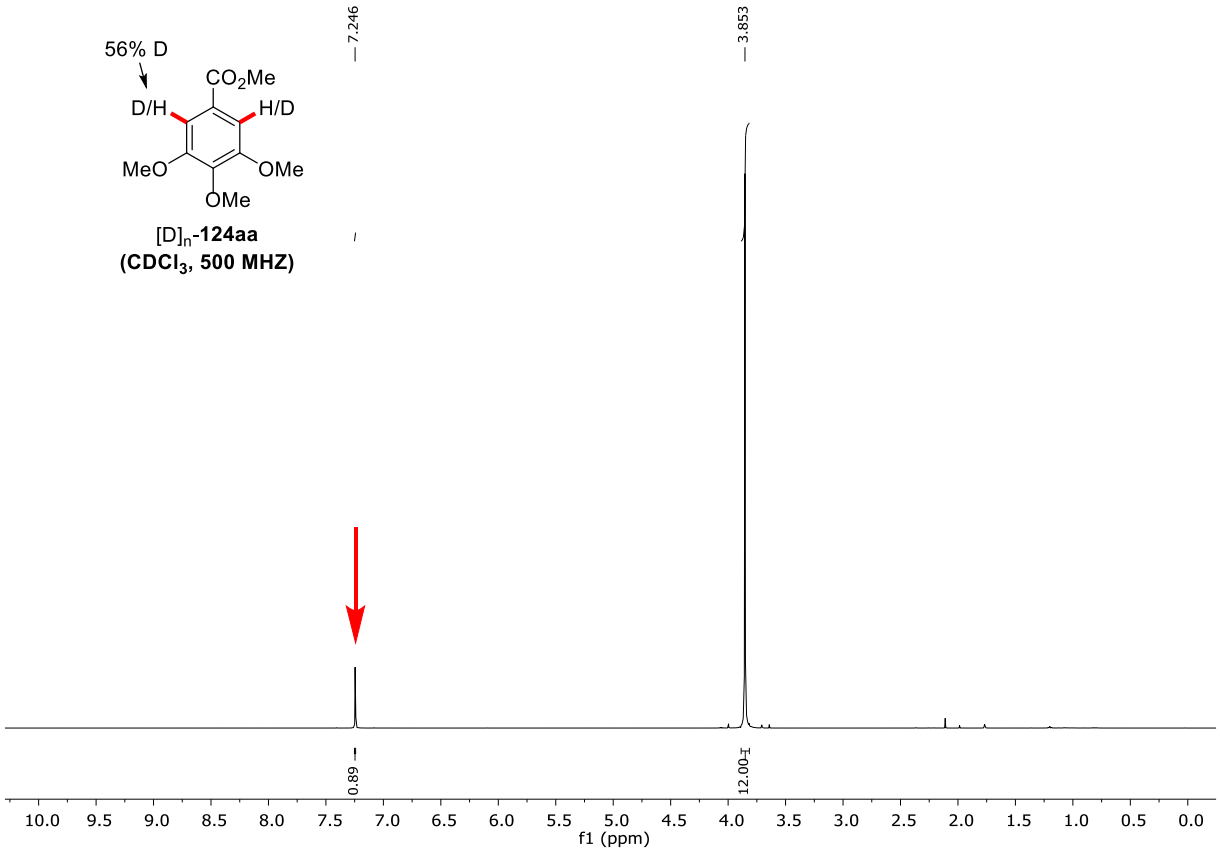
(*Z*)-3-[(Triisopropylsilyl)methylene]naphtho[1,2-c]furan-1(3*H*)-one (140c): A suspension of [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %), X-phos (23.8 mg, 10 mol %), K_2CO_3 (138 mg, 1.00 mmol), benzoic acid **124g** (86 mg, 0.50 mmol), and (bromoethynyl)triisopropylsilane (**33a**) (170 mg, 0.65 mmol, 1.30 equiv) in NMP (2.0 mL) was stirred under N_2 for 16 h at 120 °C. At ambient temperature, the mixture was diluted with MTBE (120 mL), then sequentially washed with H_2O (20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) to yield **140c** (123 mg, 70%) as a colorless solid.
M. p. = 131−132 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.93–8.83 (m, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.77–7.66 (m, 2H), 7.60 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 5.71 (s, 1H), 1.38 (dq, *J* = 14.3, 7.4 Hz, 3H), 1.13 (d, *J* = 7.4 Hz, 18H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 167.6 (C_q), 156.8 (C_q), 139.6 (C_q), 135.4 (CH), 133.9 (C_q), 129.2 (CH), 128.6 (C_q), 128.4 (CH), 127.6 (CH), 124.2 (CH), 119.2 (C_q), 117.2 (CH), 102.6 (CH), 18.8 (CH_3), 11.7 (CH). **IR** (ATR): 2940, 2862, 1755, 1633, 1458, 1111, 963, 751 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 375 (30) [M+Na$^+$], 353 (10) [M+H$^+$], 117 (100). **HR-MS** (ESI) *m/z* calcd for $C_{22}H_{29}O_2Si$ [M+H$^+$] 353.1931, found 353.1938.
The analytical data are in accordance with those previously reported in the literature.[146]

Mechanistic Studies

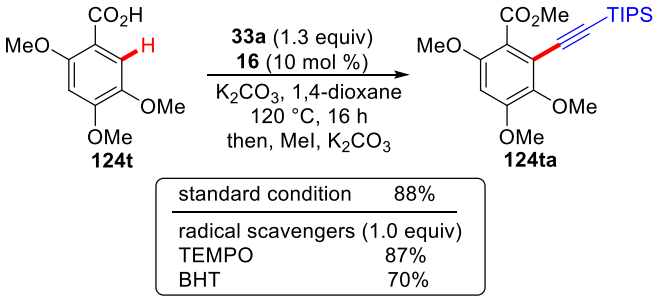
a) H/D Exchange Experiment



A suspension of 3,4,5-trimethoxybenzoic acid (**124aa**) (159 mg, 0.75 mmol), (bromoethynyl)triisopropylsilane (**33a**) (131 mg, 0.50 mmol), [Ru(O_2CMes)$_2$(*p*-cymene)] (**16**) (28.1 mg, 10 mol %), K_2CO_3 (138 mg, 1.00 mmol) in a solvent mixture of 1,4-dioxane (2.0 mL) and CD_3OD (0.1 mL) was stirred at 120 ºC for 16 h in a sealed tube under a N_2 atmosphere. At ambient temperature, MeCN (3.0 mL), K_2CO_3 (207 mg, 1.50 mmol) and MeI (355 mg, 2.50 mmol) were added and the mixture was stirred at 50 ºC for another 2 h. At ambient temperature, the mixture was dry-loaded onto silica gel and purified by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) to yield [D]$_n$-**124aa´** (90 mg, 53%) and **126aaa** (81 mg, 18%). Only trace amount of mono-alkynylation product was observed. The D-incorporation in [D]$_n$-**124aa** was estimated by ^{1}H-NMR spectroscopy.



b) Probing Radical Intermediates



Reaction in the presence of TEMPO

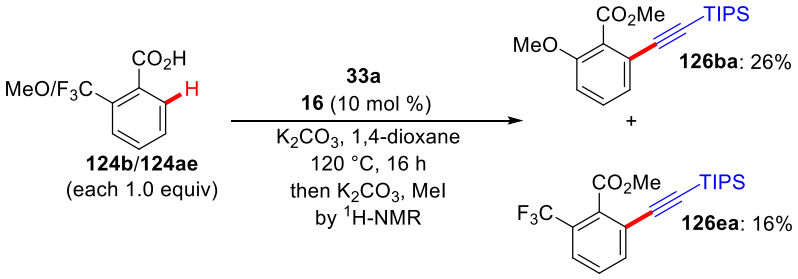
124t (106 mg, 0.5 mmol, 1.0 equiv), **33a** (170 mg, 0.65 mmol, 1.3 equiv), [Ru(O_2CMes)$_2$(*p*-cymene)] (**16**) (28.1 mg, 10 mol %), K_2CO_3 (138 mg, 1.00 mmol) and TEMPO (78 mg, 0.5 mmol, 1.0 equiv) were placed into a 25 mL Schlenk tube equipped with a septum under a N_2 atmosphere. 1,4-dioxane (2.0 mL) was introduced *via* cannula. The reaction mixture was stirred at 120 °C for 16 h. At ambient temperature, MeCN (3.0 mL), K_2CO_3 (207 mg, 1.50 mmol) and MeI (355 mg, 2.50 mmol) were added and the mixture was stirred at 50 ºC for another 2 h. At ambient temperature, the mixture was dry-loaded onto silica gel and purified by column chromatography on silica gel (*n*-hexane/EtOAc 4:1) to yield **124ta** (177 mg, 87%) as an off-white solid.

Reaction in the presence of BHT

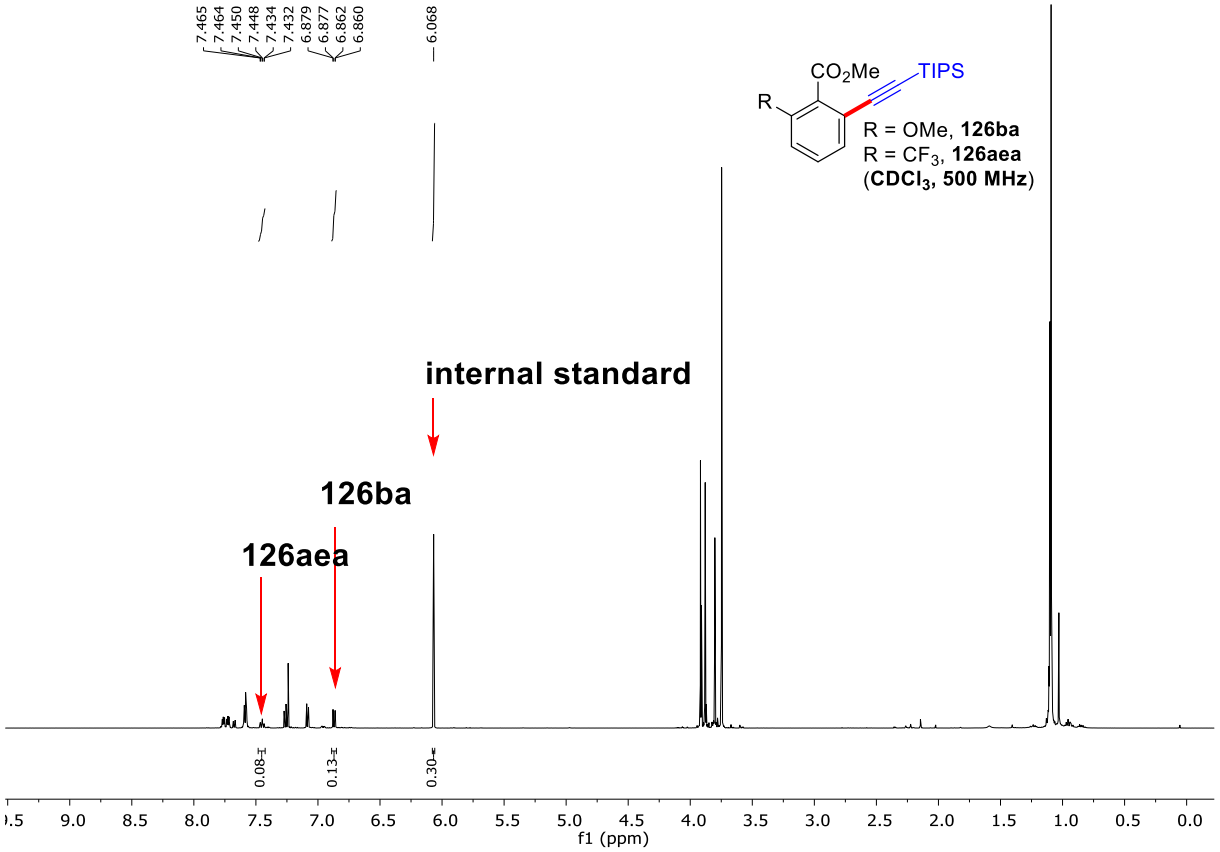
124t (106 mg, 0.5 mmol, 1.0 equiv), **33a** (170 mg, 0.65 mmol, 1.3 equiv), [Ru(O_2CMes)$_2$(*p*-cymene)] (**16**) (28.1 mg, 10 mol %), K_2CO_3 (138 mg, 1.00 mmol) and 2,6-bis(1,1-dimethylethyl)-4-methylphenol (110 mg, 0.5 mmol, 1.0 equiv) were placed into a 25 mL Schlenk tube equipped with a septum under a N_2 atmosphere. 1,4-dioxane (2.0 mL) was introduced via cannula. The reaction mixture was stirred at 120 °C for 16 h. At ambient temperature, MeCN (3.0 mL), K_2CO_3 (207 mg, 1.50 mmol) and MeI (355 mg, 2.50 mmol) were added and the mixture was stirred at 50 ºC for another 2 h. At ambient temperature, the mixture was dry-loaded onto silica gel and purified by column chromatography on silica gel (*n*-hexane/EtOAc 4:1) to yield **124ta** (142 mg, 70%) as an off-white solid.

c) Competition Experiment

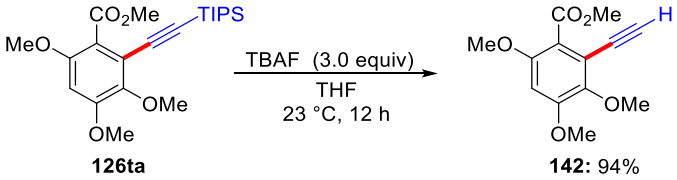
Intermolecular competition experiment between benzoic acids **124ae** and **124b**.



A suspension of (**33a**) (170 mg, 0.65 mmol, 1.3 equiv.), 2-methoxylbenzoic acid (**124b**) (76 mg, 0.50 mmol), 2-(trifluoromethyl)benzoic (**124ae**) (95 mg, 0.50 mmol), [Ru(O_2CMes)$_2$(*p*-cymene)] **16** (28.1 mg, 10 mol %), K_2CO_3 (138 mg, 1.00 mmol) in 1,4-dioxane (1.0 mL) was stirred under N_2 for 16 h at 120 ºC. At ambient temperature, MeCN (3.0 mL), K_2CO_3 (207 mg, 1.50 mmol) and MeI (355 mg, 2.50 mmol) were added and the mixture was stirred at 50 ºC for another 2 h. At ambient temperature, 1,3,5-trimethoxybenzene (16.8 mg, 0.1 mmol) was added as internal standard, the yields of **126aea** and **126ba** were determined based on crude ^{1}H-NMR analysis.



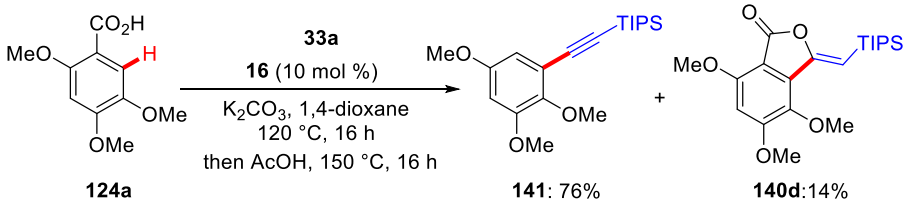
Traceless Removal of Silyl Group



Methyl 2-ethynyl-3,4,6-trimethoxybenzoate (142): **126ta** (203 mg, 0.50 mmol) was dissolved in THF (3 mL) and TBAF (1.0 M in THF, 1.50 mL) was then added at ambient temperature with constant stirring for 12 h. Then, the mixture was concentrated *in vacuo*. The residue was dissolved in H_2O (30 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to afford the alkyne **142** (118 mg, 94% yield) as an off-white solid.

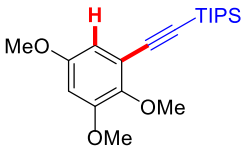
M.p. = 90–91 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 6.54 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.39 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 166.6 (C_q), 154.3 (C_q), 153.1 (C_q), 144.8 (C_q), 118.5 (C_q), 115.6 (C_q), 98.5 (CH), 84.7 (C_q), 76.5 (CH), 61.0 (CH_3), 56.5 (CH_3), 56.0 (CH_3), 52.3 (CH_3). **IR** (neat): 3265, 2950, 1721, 1585, 1269, 1208, 1027, 814, 650 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 273 (60) [M+Na^+], 251 (100) [M+H^+]. **HR-MS** (ESI) *m/z* calcd for $C_{13}H_{15}O_5$ [M+H^+] 251.0914, found 251.0922.

Decarboxylative C−H Alkynylation



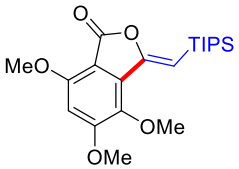
A suspension of [Ru(O_2CMes)$_2$(*p*-cymene)] (**16**) (28.1 mg, 10 mol %), K_2CO_3 (138 mg, 1.00 mmol), benzoic acid **124a** (106 mg, 0.50 mmol), and alkynyl bromide **33a** (170 mg, 0.65 mmol) in 1,4-dioxane (1.0 mL) was stirred under N_2 for 16 h at 120 ºC. At ambient temperature, the solvent was removed and AcOH (2.0 mL) was added under a N_2 atmosphere, and the mixture was stirred at 150 ºC for 16 h. At ambient temperature, the mixture was dry-loaded onto silica gel and purified by column chromatography (*n*-hexane/EtOAc) to yield the product **141** (132 mg, 76%) as a pale yellow oil and cyclic product **140d** (27 mg, 14%) as a pale yellow oil.

Triisopropyl[(2,3,5-trimethoxyphenyl)ethynyl]silane (141):



^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.47 (d, J = 2.9 Hz, 1H), 6.45 (d, J = 2.9 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 1.12 (s, 21H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 155.6 (C_q), 153.4 (C_q), 145.4 (C_q), 118.0 (C_q), 107.2 (CH), 102.8 (C_q), 101.6 (CH), 94.9 (C_q), 61.0 (CH_3), 55.9 (CH_3), 55.6 (CH_3), 18.6 (CH_3), 11.3 (CH). **IR** (neat): 2941, 2865, 2152, 1686, 1463, 1153, 1055, 882, 668 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 349 (15) [M+H$^+$], 348 (70) [M$^+$], 305 (85), 290 (100), 277 (20), 263 (30), 248 (40), 220 (30). **HR-MS** (EI) *m/z* calcd for $C_{20}H_{32}O_3Si$ [M$^+$] 348.2121, found 348.2126.

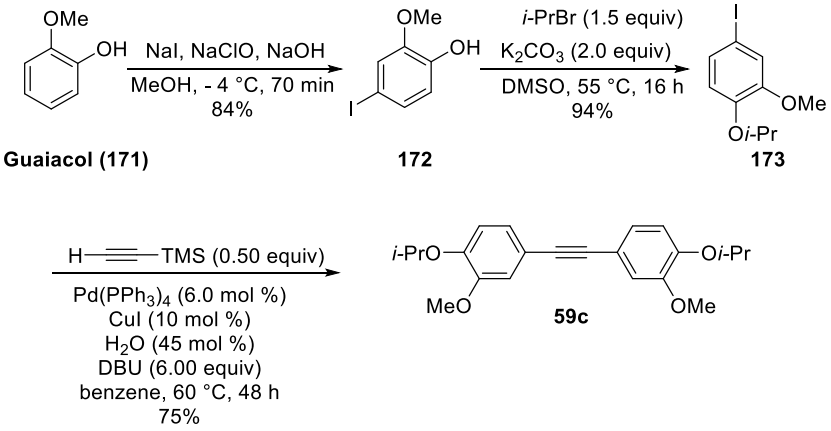
(Z)-4,5,7-Trimethoxy-3-[(triisopropylsilyl)methylene]isobenzofuran-1(3*H*)-one (140d):

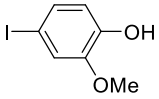


M.P. = 146–147 ºC; **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 6.48 (s, 1H), 5.95 (s, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.82 (s, 3H), 1.39–1.21 (m, 3H), 1.06 (d, J = 7.3 Hz, 18H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 164.7 (C_q), 159.4 (C_q), 155.1 (C_q), 153.6 (C_q), 137.8 (C_q), 132.0 (C_q), 105.4 (CH), 104.8 (C_q), 97.8 (CH), 59.9 (CH_3), 56.6 (CH_3), 56.4 (CH_3), 18.8 (CH_3), 11.6 (CH). **IR** (neat): 2938, 2863, 1763, 1602, 1505, 1323, 1231, 1043, 967 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 393 (30) [M+H$^+$], 392 (80) [M$^+$], 391 (15), 378 (20), 377 (100), 361 (30). **HR-MS** (EI) *m/z* calcd for $C_{21}H_{33}O_5Si$ [M$^+$] 393.2092, found 393.2099.

5.3.3 Concise Synthesis of Lamellarin Alkaloids by C−H/N−H Activation

Synthesis of 1,2-bis(4-isopropoxy-3-methoxyphenyl)ethyne (59c):

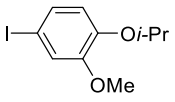




4-Iodo-2-methoxyphenol (172): Guaiacol (12.4 g, 100 mmol) was dissolved in MeOH (200 mL), then NaI (22.5 g, 149.5 mmol) and NaOH (6.25 g, 150 mmol) were added. Aqueous NaClO solution (15%, 200 mL, 145 mmol) was added dropwise over 40 min at –4 ºC. The mixture was stirred for additional 30 min at this temperature. The mixture was acidified with a HCl solution (4 M) to pH = 7, then $Na_2S_2O_3$ (10%, 60 mL) was added. MeOH was removed under reduced pressure and the aqueous phase was extracted with EtOAc (3×150 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (2×100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated. The residue was filtrated through a short pad of silica gel and further purified by vacuum distillation to give the product **172** (21.0 g, 84%) as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.16 (dd, J = 8.3, 1.9 Hz, 1H), 7.09 (d, J = 1.9 Hz, 1H), 6.66 (d, J = 8.3 Hz, 1H), 5.54 (s, 1H), 3.86 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 147.3 (C_q), 145.6 (C_q), 130.4 (CH), 119.7 (CH), 116.4 (CH), 80.9 (C_q), 56.2 (CH_3). **IR** (neat): 3489, 2941, 2838, 1601, 1491, 1440, 1218, 1020 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 250 (100) [M^+], 234 (50), 206 (30), 179 (5), 126 (10), 108 (10). **HR-MS** (ESI) *m/z* calcd for $C_7H_7IO_2$ [M^+] 249.9491, found 249.9495.

The analytical data are in accordance with those previously reported in the literature.[147]

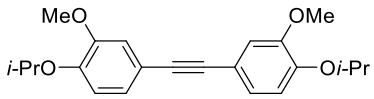


4-Iodo-1-isopropoxy-2-methoxybenzene (173): To a suspension of **172** (12.5 g, 50 mmol) and K_2CO_3 (13.8 g, 100 mmol) in DMSO (200 mL) was added *i*-PrBr (9.20 g, 75 mmol) at ambient temperature and the

mixture was heated at 55 ºC for 16 h. At ambient temperature, the mixture was diluted with EtOAc (500 mL) and washed with H_2O (4×100 mL) and brine (100 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (*n*-hexane/EtOAc, 20/1) to give the product **173** (13.7 g, 94%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.17 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.10 (d, *J* = 2.1 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.46 (hept, *J* = 6.1 Hz, 1H), 3.81 (s, 3H), 1.33 (d, *J* = 6.1 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 151.3 (C_q), 147.4 (C_q), 129.7 (CH), 121.1 (CH), 117.6 (CH), 82.8 (C_q), 71.6 (CH), 56.1 (CH_3), 22.0 (CH_3). **IR** (neat): 2974, 1578, 1489, 1245, 1220, 1134, 1025, 824 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 292 (30) [M^+], 249 (100), 234 (50), 217 (5), 206 (15), 190 (5). **HR-MS** (EI) *m/z* calcd for $C_{10}H_{13}IO_2$ [M^+] 291.9960, found 291.9953.

The analytical data are in accordance with those previously reported in the literature.[122f]

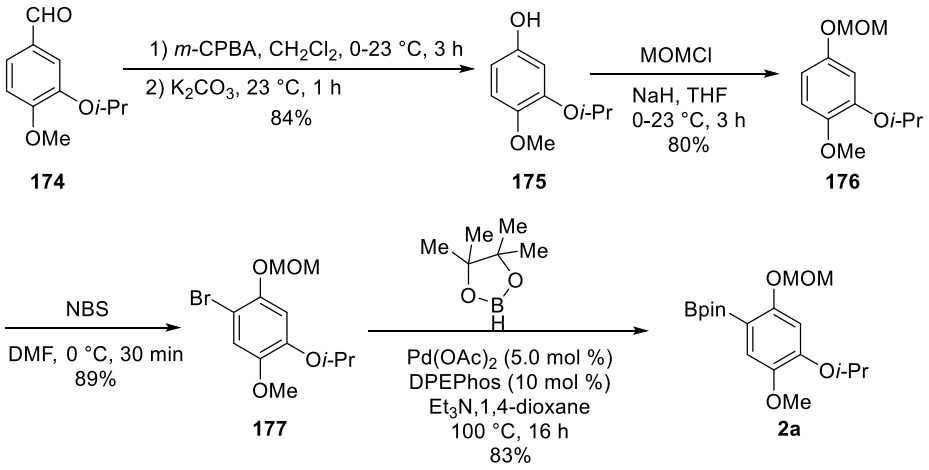


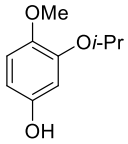
1,2-Bis(4-isopropoxy-3-methoxyphenyl)ethyne (59c): Aryl iodide **173** (8.70 g, 30 mmol), $Pd(PPh_3)_4$ (1.04 g, 6 mol %), CuI (285 mg, 10 mol %) were placed into a 250 mL Schlenk flask under a N_2 atmosphere. Benzene (80 mL) and DBU (27 mL, 180 mmol) were added *via* cannula. Degassed H_2O (121 mg, 45 mol %) and ethynyltrimethylsilane (2.10 mL, 15 mmol) were added by syringe sequentially. The mixture was kept in dark by aluminum foil and stirred at 60 ºC for 48 h. At ambient temperature, the mixture was diluted with CH_2Cl_2 (400 mL) and washed with HCl (3 M, 3×75 mL), sat. aq. NH_4Cl/NH_3 (1/1, 3×75 mL) and brine (75 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc 4/1 to CH_2Cl_2) to afford the product **59c** (3.99 g, 75%) as a white solid.

M. **p**. = 176−177 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.06 (dd, *J* = 8.2, 1.9 Hz, 2H), 7.01 (d, *J* = 1.9 Hz, 2H), 6.82 (d, *J* = 8.2 Hz, 2H), 4.53 (hept, *J* = 6.1 Hz, 2H), 3.84 (s, 6H), 1.35 (d, *J* = 6.1 Hz, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 149.8 (C_q), 147.6 (C_q), 124.5 (CH), 115.7 (C_q), 115.0 (CH), 114.8 (CH), 88.0 (C_q), 71.3 (CH), 55.9 (CH_3), 22.0 (CH_3). **IR** (neat): 2976, 2916, 1509, 1241, 1214, 1135, 1036, 852 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 355 (10) [M+H^+], 354 (30) [M^+], 312 (15), 270 (100), 255 (20), 227 (20). **HR-MS** (EI) *m/z* calcd for $C_{22}H_{26}O_4$ [M^+] 354.1831, found 354.1828.

The analytical data are in accordance with those previously reported in the literature.[148]

Synthesis of 2-[4-isopropoxy-5-methoxy-2-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2a)

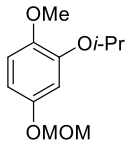




3-Isopropoxy-4-methoxyphenol (175): Under an argon atmosphere, *m*-CPBA (70%, 11.8 g, 48 mmol) was added portionwise to a solution of **174** (7.77 g, 40 mmol) in CH_2Cl_2 (120 mL) at 0 °C. After being stirred at 23 °C for 3 h, to the mixture was added saturated aqueous $NaHCO_3$ (80 mL). The mixture was diluted with H_2O (50 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3×80 mL). The combined extract was washed with brine (100 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in MeOH (200 mL) and K_2CO_3 (13.8 g, 100 mmol) was added portionwise to the solution. After being stirred for 1 h, the mixture was evaporated under reduced pressure. H_2O (150 mL) was added to the residue and the aqueous solution was extracted with EtOAc (3×100 mL). The extract was washed with brine (100 mL), dried over Na_2SO_4, evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 15:1) to yield **175** (6.12 g, 84%) as a colorless solid.

M. p. = 124−125 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.71 (d, J = 8.6 Hz, 1H), 6.45 (d, J = 2.8, 1H), 6.33 (dd, J = 8.6, 2.8 Hz, 1H), 4.42 (hept, J = 6.1 Hz, 1H), 3.76 (s, 3H), 1.30 (d, J = 6.1 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 150.2 (C_q), 148.1 (C_q), 144.2 (C_q), 113.5 (CH), 106.5 (CH), 104.1 (CH), 71.3 (CH), 56.8 (CH_3), 21.9 (CH_3). **IR** (neat): 3424, 2977, 1606, 1504, 1460, 1287, 1221, 1126 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 183 (10) [M+H$^+$], 182 (50) [M$^+$], 140 (70), 125 (100), 111 (10), 97 (30). **HR-MS** (EI) *m/z* calcd for $C_{10}H_{14}O_3$ [M$^+$] 182.0943, found 182.0944.

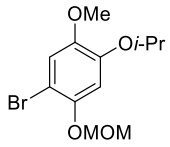
The analytical data are in accordance with those previously reported in the literature.[122i]



2-Isopropoxy-1-methoxy-4-(methoxymethoxy)benzene (176): Under argon, a solution of **175** (3.64 g, 20 mmol) in THF (20 mL) was added dropwise to A suspension of NaH (60%, 2.40 g, 60 mmol) in THF (30 mL) at 0 °C. After being stirred for 30 min, chloromethyl methyl ether (2.41 g, 30 mmol) was added and the mixture was stirred for 2 h at 0 °C and additional 1 h at ambient temperature. To the mixture was added saturated aqueous NH_4Cl (80 mL) and extracted with EtOAc (3×80 mL). The extract was washed with brine (80 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (*n*-hexane/EtOAc 10/1) to give **176** as a colorless oil (3.62 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.76 (d, *J* = 8.8 Hz, 1H), 6.63 (d, *J* = 2.8 Hz, 1H), 6.57 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.08 (s, 2H), 4.48 (hept, *J* = 6.1 Hz, 1H), 3.79 (s, 3H), 3.46 (s, 3H), 1.35 (d, *J* = 6.1 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 151.6 (C_q), 148.1 (C_q), 145.6 (C_q), 112.8 (CH), 107.5 (CH), 105.9 (CH), 95.3 (CH_2), 71.4 (CH), 56.6 (CH_3), 55.9 (CH_3), 22.0 (CH_3). **IR** (neat): 2975, 2931, 1595, 1503, 1224, 1150, 1009, 920 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 227 (10) [M+H$^+$], 226 (80) [M$^+$], 195 (10), 184 (60), 154 (80), 139 (100). **HR-MS** (EI) *m/z* calcd for $C_{12}H_{18}O_4$ [M$^+$] 226.1205, found 226.1213.

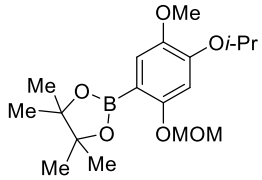
The analytical data are in accordance with those previously reported in the literature.[122i]



1-Bromo-4-isopropoxy-5-methoxy-2-(methoxymethoxy)benzene (177): A solution of NBS (2.8 g, 15.7 mmol) in DMF (20 mL) was added dropwise to a solution of **176** (3.39 g, 15 mmol) in DMF (15 mL) at 0 °C. After being stirred for 30 min, to the reaction mixture was added H_2O (30 mL) at the same temperature and allowed to warm to ambient temperature. The mixture was diluted with Et_2O (250 mL), washed with H_2O (3×40 mL) and brine (80 mL). The organic phase was dried over Na_2SO_4 and concentrated at ambient temperature. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 10/1) to yield **S7** (4.07 g, 89%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.00 (s, 1H), 6.79 (s, 1H), 5.12 (s, 2H), 4.46 (hept, *J* = 6.1 Hz, 1H), 3.79 (s, 3H), 3.51 (s, 3H), 1.33 (d, *J* = 6.1 Hz, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 147.8 (C_q), 147.1 (C_q), 146.4 (C_q), 116.6 (CH), 107.0 (CH), 103.2 (C_q), 96.3 (CH_2), 72.1 (CH), 56.7 (CH_3), 56.4 (CH_3), 22.0 (CH_3). **IR** (neat): 2974, 2903, 2833, 1495, 1374, 1206, 1149, 1010 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 304 (10) [M$^+$], 262 (10), 232 (30), 217 (20), 189 (10), 43 (100). **HR-MS** (EI) *m/z* calcd for $C_{12}H_{17}{}^{79}BrO_4$ [M$^+$] 304.0310, found 304.0310; $C_{12}H_{17}{}^{81}BrO_4$ [M$^+$] 306.0290, found 306.0290.

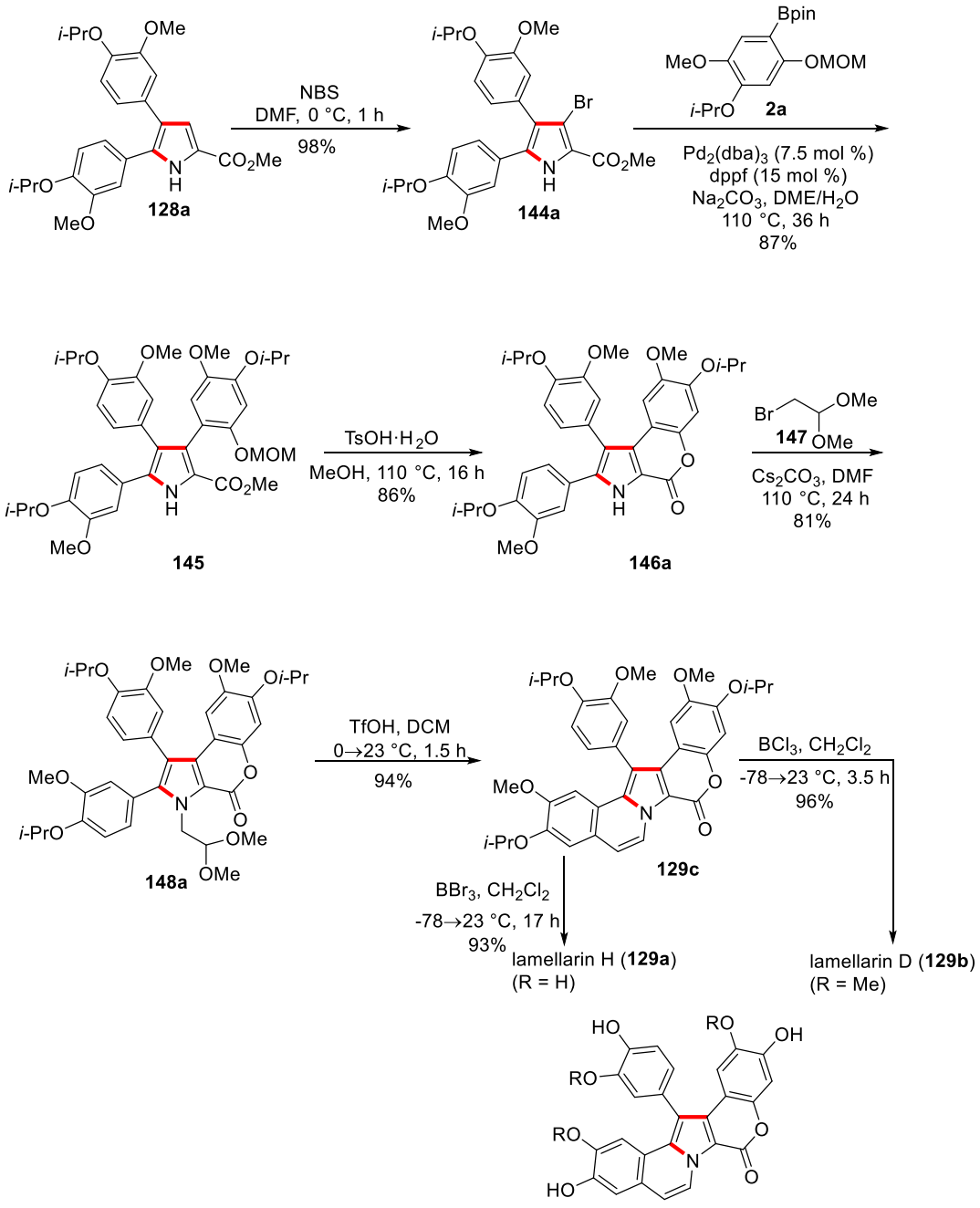
The analytical data are in accordance with those previously reported in the literature.[122i]

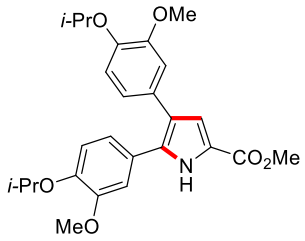


2-[4-Isopropoxy-5-methoxy-2-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2a): A mixture of **177** (3.05 g, 10 mmol), Et_3N (5.6 mL, 40 mmol), $Pd(OAc)_2$ (112 mg, 5 mol %), DPEphos (538 mg, 10 mol %), and **178** (3.84 g, 30 mmol) in 1,4-dioxane (20 mL) was heated at 100 °C for 16 h. At ambient temperature, to the mixture was added saturated NH_4Cl (80 mL), and the aqueous solution was extracted with EtOAc (3×60 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (*n*-hexane/EtOAc/Et_3N 100/10/1) to give **2a** (2.92 g, 83%) as a pale yellow oil.

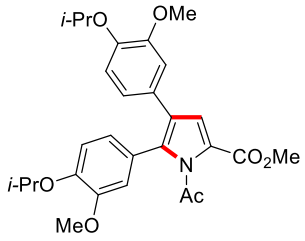
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.14 (s, 1H), 6.61 (s, 1H), 5.04 (s, 2H), 4.51 (hept, J = 6.1 Hz, 1H), 3.79 (s, 3H), 3.48 (s, 3H), 1.31 (d, J = 6.1 Hz, 6H), 1.27 (s, 12H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 157.2 (C_q), 150.5 (C_q), 145.3 (C_q), 119.0 (CH), 106.1 (CH), 97.1 (CH_2), 83.0 (C_q), 70.9 (CH), 56.3 (CH_3), 56.0 (CH_3), 24.6 (CH_3), 21.7 (CH_3). **IR** (neat): 2976, 2933, 1602, 1507, 1370, 1346, 1202, 1141 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 353 (10) [$M+H^+$], 352 (100) [M^+], 310 (10), 278 (30), 236 (30), 194 (80). **HR-MS** (EI) *m/z* calcd for $C_{18}H_{29}BO_6$ [M^+] 352.2057, found 352.2062.

Synthetic Route to Lamellarins D and H:





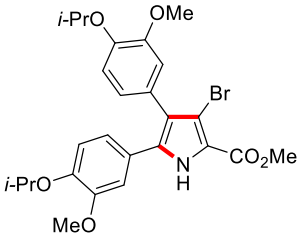
Methyl 4,5-bis(4-isopropoxy-3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (128a): Methyl 2-acetamidoacrylate (**127**) (787 mg, 5.50 mmol), 1,2-bis(4-isopropoxy-3-methoxy-phenyl)ethyne (**59c**) (1.77 g, 5.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (153 mg, 5.0 mol %), $AgSbF_6$ (343 mg, 20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (2.00 g, 10.0 mmol) was placed into a 100 mL sealed tube under a N_2 atmosphere. A solvent mixture of MeOH/DCE (20 mL/10 mL) was added *via* cannula. The reaction mixture was stirred at 110 °C for 24 h. At ambient temperature, the reaction mixture was dry-loaded onto silica gel and purified by column chromatography (*n*-hexane/EtOAc 4/1 to 2/1) to afford the desired product **128a** (2.11g, 93%) as colorless solid. **M. p.** = 70−71 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.16 (s, 1H), 7.01 (d, J = 2.7 Hz, 1H), 6.93 (dd, J = 8.2, 2.1 Hz, 1H), 6.87–6.77 (m, 5H), 4.56–4.43 (m, 2H), 3.84 (s, 3H), 3.67 (s, 3H), 3.63 (s, 3H), 1.35 (d, J = 6.1 Hz, 6H), 1.34 (d, J = 6.1 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 161.6 (C_q), 150.1 (C_q), 150.1 (C_q), 147.2 (C_q), 145.9 (C_q), 133.1 (C_q), 128.6 (C_q), 124.8 (C_q), 123.5 (C_q), 121.4 (C_q), 120.7 (CH), 120.1 (CH), 116.5 (CH), 115.9 (CH), 115.5 (CH), 112.6 (CH), 112.0 (CH), 71.5 (CH), 71.4 (CH), 55.8 (CH_3), 55.7 (CH_3), 51.5 (CH_3), 22.1 (CH_3), 22.0 (CH_3). **IR** (neat): 3296, 2975, 2934, 1680, 1517, 1465, 1204, 1106, 765 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 454 (100) $[M+H^+]$, 453 (80) $[M^+]$, 411 (30), 369 (100), 337 (80). **HR-MS** (EI) *m/z* calcd for $C_{26}H_{31}NO_6$ $[M^+]$ 453.2151, found 453.2151.



Methyl 1-acetyl-4,5-bis(4-isopropoxy-3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (128a'): Characterization data of **128a'**.

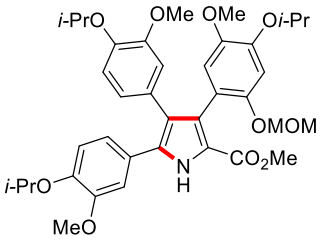
M. p. = 143−144 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.14 (s, 1H), 6.88–6.84 (m, 2H), 6.82 (s, 1H), 6.78–6.72 (m, 2H), 6.63 (s, 1H), 4.55 (hept, J = 6.1 Hz, 1H), 4.46 (hept, J = 6.1 Hz, 1H), 3.87 (s, 3H), 3.72 (s, 3H), 3.56 (s, 3H), 2.31 (s, 3H), 1.37 (d, J = 6.1 Hz, 6H), 1.33 (d, J = 6.1 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 174.1 (C_q), 161.1 (C_q), 150.0 (C_q), 149.8 (C_q), 147.8 (C_q), 145.9 (C_q), 134.1 (C_q), 127.1 (C_q), 124.4 (C_q), 123.4 (CH), 123.2 (C_q), 122.5 (C_q), 120.1 (CH), 117.9 (CH), 115.6 (CH), 114.9 (CH), 114.6 (CH), 111.8 (CH), 71.3 (CH), 71.2 (CH), 56.0 (CH_3), 55.5 (CH_3), 51.8 (CH_3), 28.8 (CH_3), 22.1 (CH_3), 22.0 (CH_3). **IR** (neat): 2983, 2934, 2827, 1749, 1691, 1470, 1227, 850, 769 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 496 (10) $[M+H^+]$, 495 (40)

[M$^+$], 453 (60), 411 (40), 369 (100), 337 (60). **HR-MS** (EI) *m/z* calcd for $C_{28}H_{33}NO_7$ [M$^+$] 495.2257, found 495.2265.



Methyl 3-bromo-4,5-bis(4-isopropoxy-3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (144a): to a solution of **128a** (1.40g, 3.09 mmol) in DMF (40 mL) was added a solution of NBS (555 mg, 3.12 mmol) in DMF (5 mL) dropwise within 10 min at 0 °C under a N_2 atmosphere. The reaction mixture was stirred at 0 °C for 1 h. Then, the mixture was diluted with EtOAc (200 mL) and washed with H_2O (3×60 mL) and brine (60 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography over silica gel (*n*-hexane/EtOAc 5/1) to give **144a** (1.61g, 98%) as a colorless solid.

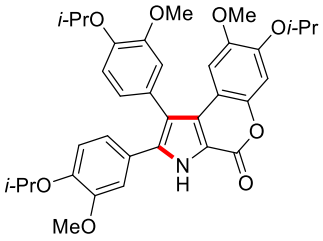
M. p. = 71−72 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 9.37 (s, 1H), 6.91–6.75 (m, 5H), 6.69 (d, *J* = 2.0 Hz, 1H), 4.59–4.45 (m, 2H), 3.90 (s, 3H), 3.73 (s, 3H), 3.54 (s, 3H), 1.37 (d, *J* = 6.1 Hz, 6H), 1.34 (d, *J* = 6.1 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.9 (C_q), 149.8 (C_q), 149.7 (C_q), 147.1 (C_q), 146.4 (C_q), 133.6 (C_q), 126.3 (C_q), 124.2 (C_q), 123.6 (C_q), 123.1 (CH), 119.5 (CH), 118.9 (C_q), 115.2 (CH), 115.0 (CH), 114.6 (CH), 111.5 (CH), 106.0 (C_q), 71.1 (CH), 71.1 (CH), 55.7 (CH_3), 55.4 (CH_3), 51.5 (CH_3), 21.9 (CH_3), 21.8 (CH_3). **IR** (neat): 3284, 2975, 1671, 1518, 1467, 1383, 1233, 1106, 1032 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 533 (40) [M$^+$], 489 (20), 449 (70), 417 (100), 369 (10), 308 (50). **HR-MS** (EI) *m/z* calcd for $C_{26}H_{30}{}^{79}BrNO_6$ [M$^+$] 531.1257, found 531.1256; $C_{26}H_{30}{}^{81}BrNO_6$ [M$^+$] 533.1236, found 533.1240.



Methyl 4,5-bis(4-isopropoxy-3-methoxyphenyl)-3-[4-isopropoxy-5-methoxy-2-(methoxymethoxy)phenyl]-1*H*-pyrrole-2-carboxylate (145): **144a** (1.06 g, 2.0 mmol), **2a** (1.41 g, 4.0 mmol), $Pd_2(dba)_3$ (137 mg, 7.5 mol %), dppf (166 mg, 15 mol %) and Na_2CO_3 (1.40 g, 13.2 mmol) was placed into a 100 mL sealed tube under a N_2 atmosphere. A solvent mixture of DME/H_2O (30 mL/2.4 mL) was added *via* cannula. The reaction mixture was kept in the dark and stirred at 110 °C for 24 h. After cooling down to ambient temperature, the mixture was evaporated, the residue was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (4×30 mL). The extracts was washed with brine (2×30 mL), dried over Na_2SO_4, and evaporated.

The residue was purified by column chromatography over silica gel (*n*-hexane/EtOAc 2/1) to give **145** (1.18 g, 87%) as a pale yellow solid.

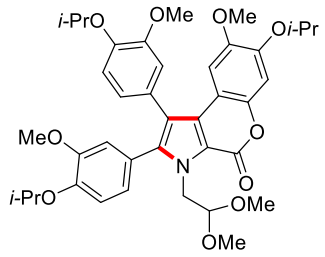
M. p. = 81−82 ºC. **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 9.23 (s, 1H), 6.92 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.78 (s, 1H), 6.78 (d, *J* = 2.1 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.61 (s, 1H), 6.53 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 1H), 4.75 (d, *J* = 6.9 Hz, 1H), 4.55–4.43 (m, 3H), 4.39 (hept, *J* = 6.1 Hz, 1H), 3.68 (s, 3H), 3.62 (s, 3H), 3.54 (s, 3H), 3.44 (s, 3H), 3.21 (s, 3H), 1.34 (d, *J* = 6.1 Hz, 12H), 1.27 (d, *J* = 6.1 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 161.7 (C_q), 149.9 (C_q), 149.8 (C_q), 149.8 (C_q), 147.1 (C_q), 147.0 (C_q), 145.4 (C_q), 145.0 (C_q), 132.4 (C_q), 128.0 (C_q), 127.7 (C_q), 124.7 (C_q), 123.7 (C_q), 122.5 (CH), 119.6 (CH), 118.8 (C_q), 117.1 (C_q), 116.1 (CH), 115.7 (CH), 115.3 (CH), 114.3 (CH), 112.0 (CH), 105.6 (CH), 96.5 (CH_2), 71.4 (CH), 71.3 (CH), 71.3 (CH), 56.4 (CH_3), 55.6 (CH_3), 55.5 (CH_3), 55.4 (CH_3), 51.3 (CH_3), 22.0 (CH_3), 22.0 (CH_3). **IR** (neat): 3530, 3314, 2976, 1670, 1506, 1440, 1214, 1107, 751 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 678 (50) [M+H$^+$], 677 (100) [M$^+$], 602 (30), 588 (10), 560 (10), 528 (10). **HR-MS** (ESI) *m/z* calcd for $C_{38}H_{48}NO_{10}$ [M+H$^+$] 678.3273, found 678.3264.



7-Isopropoxy-1,2-bis(4-isopropoxy-3-methoxyphenyl)-8-methoxychromeno[3,4-b]pyrrol-4(3*H*)-one (146a): Under N_2, **145** (1.02 g, 1.50 mmol), $TsOH{\cdot}H_2O$ (71 mg, 25 mol %) was placed into a 100 mL sealed tube. MeOH (20 mL) was added *via* cannula. The reaction mixture was stirred at 110 °C for 16 h. At ambient temperature, 40 mL saturated $NaHCO_3$ solution was carefully added. A large amount of precipitate formed during this process. The solid was collected by filtration and further washed with cold H_2O (2×5.0 mL) and *n*-hexane (2×5.0 mL). The obtained pale brown solid **146a** (776 mg, 86%) was analytic pure and didn't need further purification.

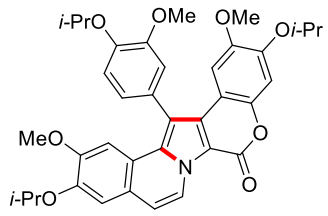
M. p. = 223−224 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 10.49 (s, 1H), 7.08 (d, *J* = 2.1 Hz, 1H), 7.05–6.94 (m, 3H), 6.94 (d, *J* = 1.7 Hz, 1H), 6.90 (s, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 6.77 (s, 1H), 4.61–4.48 (m, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.45 (s, 3H), 1.38 (d, *J* = 6.1 Hz, 12H), 1.35 (d, *J* = 6.1 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 156.1 (C_q), 150.9 (C_q), 150.0 (C_q), 147.5 (C_q), 147.2 (C_q), 146.8 (C_q), 146.7 (C_q), 146.1 (C_q), 139.1 (C_q), 129.0 (C_q), 127.9 (C_q), 123.5 (CH), 123.5 (C_q), 120.0 (CH), 117.2 (C_q), 116.5 (CH), 115.0 (C_q), 114.8 (CH), 114.8 (CH), 111.3 (CH), 110.6 (C_q), 105.0 (CH), 103.8 (CH), 71.6 (CH), 71.5 (CH), 71.2 (CH), 56.1 (CH_3), 55.7 (CH_3), 55.5 (CH_3), 22.0 (CH_3), 21.8 (CH_3). **IR** (neat): 3275, 2972, 1685, 1521, 1460, 1257, 1146, 870, 642 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 624 (100) [M+Na$^+$], 602 (80) [M+H$^+$], 563 (10), 525 (20), 481 (30), 437 (50). **HR-MS** (ESI) *m/z* calcd for $C_{35}H_{40}NO_8$ [M+H$^+$] 602.2748, found 602.2747.

The analytical data are in accordance with those previously reported in the literature.[148]



3-(2,2-Dimethoxyethyl)-7-isopropoxy-1,2-bis(4-isopropoxy-3-methoxyphenyl)-8-methoxychromeno[3,4-b]pyrrol-4(3*H*)-one (148a): Under N_2, **146a** (867 mg, 1.44 mmol) and Cs_2CO_3 (3.05 g, 9.36 mmol) were placed in a 100 mL sealed tube. 2-Bromo-1,1-dimethoxyethane (**147**) (1.60 g, 9.5 mmol) and DMF (30 mL) were added *via* cannula. The reaction mixture was stirred at 110 °C for 24 h. At ambient temperature, the mixture was diluted with EtOAc (250 mL) and washed with H_2O (3×60 mL) and brine (60 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography over silica gel (*n*-hexane/EtOAc 5/1) to give **148a** (804 mg, 81%) as a colorless solid.

M. **p**. = 162−163 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 6.92 (s, 1H), 6.91 (s, 1H), 6.92–6.78 (m, 4H), 6.79 (d, *J* = 8.8 Hz, 1H), 6.71 (d, *J* = 1.1 Hz, 1H), 4.85 (t, *J* = 5.5 Hz 1H), 4.62–4.41 (m, 5H), 3.65 (s, 3H), 3.63 (s, 3H), 3.45 (s, 3H), 3.31 (s, 6H), 1.38 (d, *J* = 6.1 Hz, 6H), 1.33 (d, *J* = 6.1 Hz, 6H), 1.31 (d, *J* = 6.1 Hz, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 155.6 (C_q), 150.1 (C_q), 149.5 (C_q), 147.4 (C_q), 147.2 (C_q), 146.5 (C_q), 146.2 (C_q), 146.1 (C_q), 144.0 (C_q), 127.7 (C_q), 127.4 (C_q), 123.8 (CH), 123.4 (CH), 122.2 (C_q), 118.5 (C_q), 115.9 (CH), 115.2 (CH), 115.0 (CH), 114.6 (C_q), 114.5 (CH), 110.2 (C_q), 105.3 (CH), 104.4 (CH), 103.5 (CH), 71.5 (CH), 71.5 (CH), 71.2 (CH), 55.9 (CH_3), 55.8 (CH_3), 55.6 (CH_3), 55.3 (CH_3), 47.9 (CH_2), 22.1 (CH_3), 21.9 (CH_3). **IR** (neat): 2975, 2931, 1703, 1517, 1463, 1257, 1107, 1031, 752 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 712 (100) [M+Na$^+$], 690 (50) [M+H$^+$], 658 (80). **HR-MS** (ESI) *m/z* calcd for $C_{39}H_{48}NO_{10}$ [M+H$^+$] 690.3273, found 690.3267.

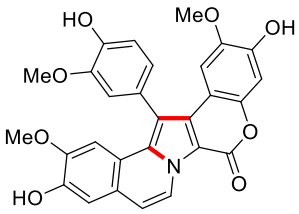


3,11-Diisopropoxy-14-(4-isopropoxy-3-methoxyphenyl)-2,12-dimethoxy-6*H*-chromeno[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (129c): Under N_2, a solution of TfOH in CH_2Cl_2 (1.0 M, 1.1 mL, 1.10 mmol) was added dropwise to a solution of **148a** (508 mg, 0.73 mmol) in CH_2Cl_2 (25 mL) within 10 min at 0 ºC. After stirring at 0 ºC for 30 min, the mixture was warmed to 23 ºC and stirred for additional 1 h. $NaHCO_3$ (919 mg, 11 mmol) and EtOH (10 mL) were added sequentially. Then, the solvent

was removed and the residue was dry-loaded no silica gel and purified by column chromatography on silica gel (*n*-hexane/EtOAc 4/1) to yield **129c** (429 mg, 94%) as a colorless solid.

M. **p**. = 190−191 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.08 (d, *J* = 7.3 Hz, 1H), 7.12–7.11 (m, 2H), 7.10–7.09 (m, 2H), 7.02 (s, 1H), 6.91 (d, *J* = 7.3 Hz, 1H), 6.85 (s, 1H), 6.70 (s, 1H), 4.67–4.54 (m, 2H), 4.47 (hept, *J* = 6.1 Hz, 1H), 3.81 (s, 3H), 3.40 (s, 3H), 3.39 (s, 3H), 1. 39–1.36 (m, 12H), 1.34–1.32 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 155.2 (C_q), 151.2 (C_q), 150.0 (C_q), 148.3 (C_q), 147.6 (C_q), 147.0 (C_q), 146.4 (C_q), 146.3 (C_q), 134.1 (C_q), 129.1 (C_q), 128.6 (C_q), 124.5 (C_q), 123.8 (CH), 122.9 (CH), 118.8 (C_q), 116.8 (CH), 115.0 (CH), 112.1 (CH), 110.8 (C_q), 110.3 (CH), 109.8 (C_q), 107.6 (C_q), 105.5 (CH), 105.3 (CH), 103.2 (CH), 71.6 (CH), 71.3 (CH), 71.0 (CH), 56.1 (CH_3), 55.3 (CH_3), 55.0 (CH_3), 21.8 (CH_3), 21.8 (CH_3), 21.8 (CH_3), 21.7 (CH_3), 21.7 (CH_3), 21.7 (CH_3). **IR** (neat): 3011, 2975, 2934, 1701, 1431, 1256, 1203, 1126, 1011 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 626 (100) [M+H$^+$], 524 (5), 348 (10). **HR-MS** (ESI) *m/z* calcd for $C_{37}H_{40}NO_8$ [M+H$^+$] 626.2748, found 626.2744.

The analytical data are in accordance with those previously reported in the literature.[148]

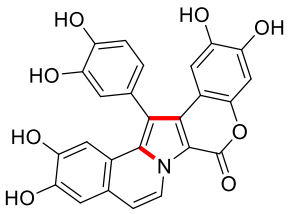


3,11-Dihydroxy-14-(4-hydroxy-3-methoxyphenyl)-2,12-dimethoxy-6*H*-chromeno[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (129b): To a solution of **129c** (94 mg, 0.15 mmol) in CH_2Cl_2 (10 mL) was added BCl_3 (1.4 mL, 1.0 M in CH_2Cl_2, 1.40 mmol) under a N_2 atmosphere at –78 ºC. After being stirred for 30 min at this temperature, the reaction mixture was allowed to warm to ambient temperature and stirred for additional 3 h. To the mixture was added saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (4×20 mL). The extract was washed with brine (20 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1/0 to 10/1) to yield **129b** (72 mg, 96%) as a pale green solid.

M. **p**. >300 ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 9.92 (s, 1H), 9.81 (s, 1H), 9.32 (s, 1H), 8.98 (d, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.17 (s, 1H), 7.15 (d, *J* = 1.9 Hz, 1H), 7.13 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.86 (s, 1H), 6.71 (s, 1H), 3.77 (s, 3H), 3.38 (s, 3H), 3.38 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ = 154.0 (C_q), 148.4 (C_q), 148.2 (C_q), 148.0 (C_q), 147.6 (C_q), 146.6 (C_q), 146.1 (C_q), 144.3 (C_q), 133.8 (C_q), 128.7 (C_q), 125.3 (C_q), 124.4 (C_q), 123.6 (CH), 121.8 (CH), 117.4 (C_q), 116.2 (CH), 115.0 (CH), 112.1 (CH), 111.3 (CH), 110.6 (C_q), 108.2 (C_q), 106.2 (C_q), 105.7 (CH), 105.3 (CH), 103.5 (CH), 55.9 (CH_3), 55.0 (CH_3), 54.4 (CH_3). **IR** (neat): 3385, 2933, 2837, 1672, 1595, 1431, 1273, 1154, 1014, 850 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 522 (100) [M+Na$^+$], 500 (40) [M+H$^+$], 425 (10), 381 (20). **HR-MS**

(ESI) *m/z* calcd for $C_{28}H_{22}NO_8$ [M+H$^+$] 500.1340, found 500.1348; $C_{28}H_{21}NO_8Na$ [M+Na$^+$] 522.1159, found 522.1163.

The analytical data are in accordance with those previously reported in the literature.[148]

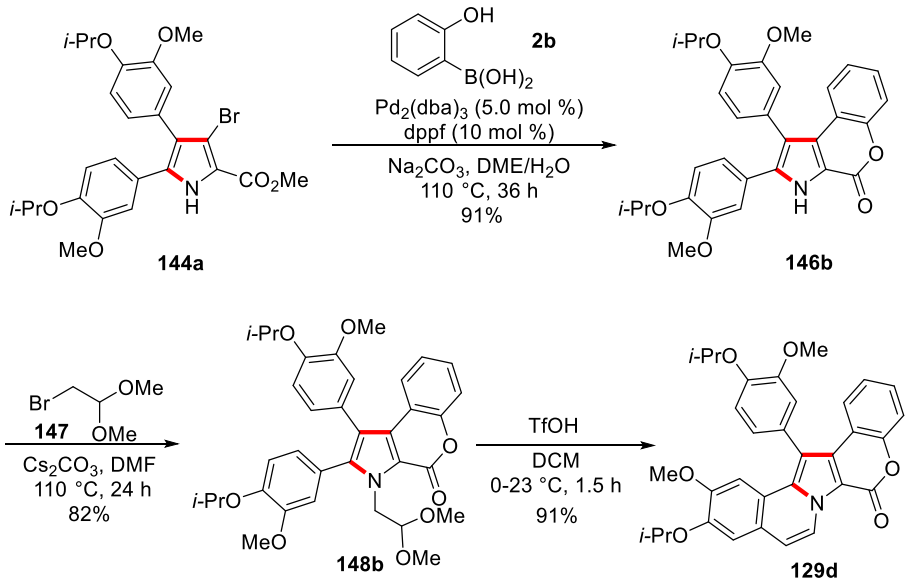


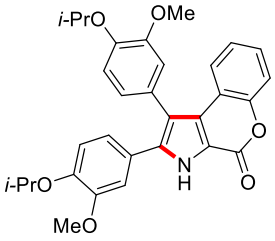
14-(3,4-Dihydroxyphenyl)-2,3,11,12-tetrahydroxy-6*H*-chromeno[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (129a): To a solution of **129c** (94 mg, 0.15 mmol) in CH_2Cl_2 (10 mL) was added BBr_3 (2.25 mL, 1.0 M in CH_2Cl_2, 2.25 mmol) under a N_2 atmosphere at –78 ºC. After being stirred for 30 min at this temperature, the reaction mixture was allowed to warm to ambient temperature and stirred for additional 16.5 h. After diluting with MeOH (5 mL), the solvent was removed under vacuum. The residue was dissolved in H_2O (20 mL) and extracted with EtOAc (4×20 mL). The extracts was washed with brine (20 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 10/1) to yield **129a** (64 mg, 93%) as a pale green solid.

M. p. >300 ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 9.98 (s_{br}, 1H), 9.76 (s_{br}, 1H), 9.41 (s_{br}, 1H), 9.19 (s_{br}, 2H), 8.99 (d, *J* = 7.4 Hz, 1H), 8.90 (s_{br}, 1H), 7.14 (d, *J* = 7.4 Hz, 1H), 7.13 (s, 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.95 (s, 1H), 6.80 (s, 1H), 6.79 (d, *J* = 2.1 Hz, 1H), 6.71 (dd, *J* = 7.9, 2.1 Hz, 1H), 6.57 (s, 1H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ = 154.2 (C_q), 147.4 (C_q), 146.6 (C_q), 146.3 (C_q), 146.0 (C_q), 145.3 (C_q), 145.1 (C_q), 141.8 (C_q), 133.7 (C_q), 128.6 (C_q), 125.3 (C_q), 123.6 (C_q), 121.3 (CH), 121.0 (CH), 117.9 (C_q), 117.4 (CH), 116.8 (CH), 112.3 (CH), 111.2 (CH), 111.2 (C_q), 109.5 (CH), 109.4 (CH), 108.7 (C_q), 106.2 (C_q), 103.2 (CH). **IR** (neat): 3363, 1670, 1428, 1274, 1153, 1030, 863, 753 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 480 (100) [M+Na$^+$], 458 (80) [M+H$^+$], 441 (30), 425 (10), 413 (5). **HR-MS** (EI) *m/z* calcd for $C_{25}H_{16}NO_8$ [M+H$^+$] 458.0870, found 458.0883; $C_{25}H_{15}NO_8Na$ [M+Na$^+$] 480.0690, found 480.0703.

The analytical data are in accordance with those previously reported in the literature.[122f]

Synthesis of Lamellarin Analogue 129d

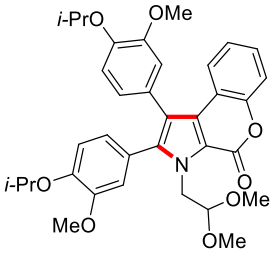




1,2-Bis(4-isopropoxy-3-methoxyphenyl)chromeno[3,4-b]pyrrol-4(3*H*)-one (146b): Under N_2, **144a** (1.06 g, 2.0 mmol), **2b** (414 mg, 3.0 mmol), $Pd_2(dba)_3$ (91.6 mg, 5.0 mol %), dppf (111 mg, 10 mol %) and Na_2CO_3 (1.40 g, 13.2 mmol) were placed into a 100 mL sealed tube. A solvent mixture of DME/H_2O (30 mL/2.4 mL) was added *via* cannula. The reaction mixture was kept in the dark and stirred at 110 °C for 36 h. After cooling down to ambient temperature, the mixture was evaporated, and the residue was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (4×30 mL). The combined organic phase was washed with brine (2×30 mL), dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel (*n*-hexane/EtOAc 3/1) to give **146b** as a colorless solid (935 mg, 91%).

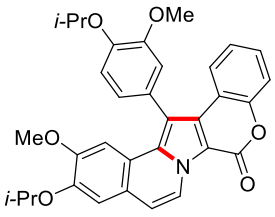
M. p. = 245−247 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 10.93 (s, 1H), 7.43–7.27 (m, 3H), 7.12 (d, J = 2.2 Hz, 1H), 7.10–6.96 (m, 3H), 7.00–6.90 (m, 2H), 6.81 (d, J = 8.5 Hz, 1H), 4.70–4.60 (m, 1H), 4.58–4.46 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 1.44 (d, J = 6.0 Hz, 6H), 1.37 (d, J = 6.1 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 155.9 (C_q), 151.4 (C_q), 150.8 (C_q), 149.9 (C_q), 147.6 (C_q), 146.9 (C_q), 139.5 (C_q), 128.4 (C_q), 127.6 (C_q), 127.5 (CH), 124.0 (CH), 123.6 (CH), 123.4 (C_q), 123.3 (CH), 120.2 (CH), 118.5 (C_q), 118.1 (C_q), 117.3 (CH), 116.0 (CH), 115.9 (C_q), 114.7 (CH), 114.5 (CH), 111.4 (CH), 71.4 (CH), 71.1 (CH), 56.1 (CH_3), 55.7 (CH_3), 22.1 (CH_3), 22.1 (CH_3). **IR** (neat): 3240, 2976, 1697, 1466, 1416, 1230, 1106, 772 cm^{-1}. **MS** (EI) *m/z* (relative

intensity) 514 (20) [M+H$^+$], 513 (40) [M$^+$], 471 (10), 429 (100), 369 (10), 337 (10), 325 (10). **HR-MS** (EI) *m/z* calcd for $C_{31}H_{31}NO_6$ [M$^+$] 513.2151, found 513.2140.



3-(2,2-Dimethoxyethyl)-1,2-bis(4-isopropoxy-3-methoxyphenyl)chromeno[3,4-b]pyrrol-4(3*H*)-one (148b): Under N_2, **146b** (514 mg, 1.0 mmol) and Cs_2CO_3 (2.11 g, 6.50 mmol) were placed into a 100 mL sealed tube. 2-Bromo-1,1-dimethoxyethane (**147**) (1.11 g, 6.60 mmol) and solvent DMF (15 mL) were added *via* cannula. The reaction mixture was stirred at 110 °C for 36 h. At ambient temperature, the mixture was diluted with EtOAc (200 mL) and washed with H_2O (3×50 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography over silica gel (*n*-hexane/EtOAc 6/1) to give **148b** as a colorless solid (493 mg, 82%).

M. p. = 169−170 ºC. **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.48 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.36 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.29–7.26 (m, 1H), 7.02–6.97 (m, 1H), 6.86–6.84 (m, 2H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.77 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.71 (d, *J* = 1.9 Hz, 1H), 4.85 (t, *J* = 5.5 Hz, 1H), 4.59–4.46 (m, 4H), 3.65 (s, 3H), 3.64 (s, 3H), 3.31 (s, 6H), 1.40–1.27 (m, 12H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 155.2 (C_q), 151.3 (C_q), 149.9 (C_q), 149.5 (C_q), 147.4 (C_q), 146.4 (C_q), 144.2 (C_q), 127.5 (CH), 127.0 (C_q), 127.0 (C_q), 123.8 (CH), 123.6 (CH), 123.5 (CH), 123.3 (CH), 122.2 (C_q), 119.5 (C_q), 118.1 (C_q), 117.0 (CH), 115.4 (C_q), 115.3 (CH), 115.3 (CH), 114.8 (CH), 114.5 (CH), 104.3 (CH), 71.3 (CH), 71.2 (CH), 55.9 (CH_3), 55.8 (CH_3), 55.4 (CH_3), 48.0 (CH_2), 22.2 (CH_3), 22.1 (CH_3). **IR** (neat): 2975, 2934, 2833, 1706, 1462, 1439, 1255, 1050 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 602 (30) [M+H$^+$], 592 (40), 570 (100), 564 (10), 550 (5). **HR-MS** (ESI) *m/z* calcd for $C_{35}H_{40}NO_8$ [M+H$^+$] 602.2748, found 602.2755.

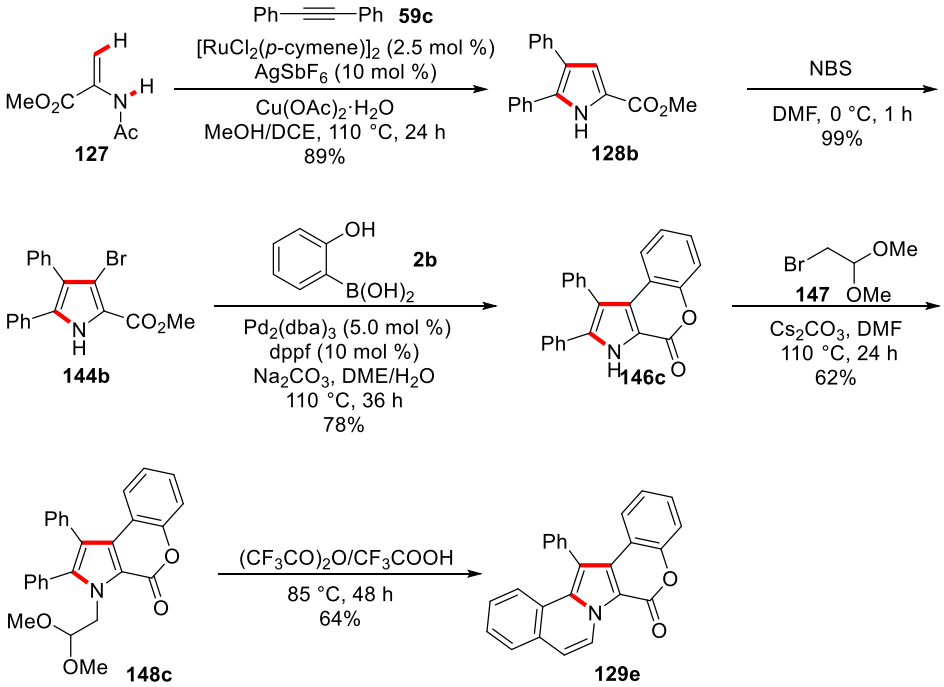


11-Isopropoxy-14-(4-isopropoxy-3-methoxyphenyl)-12-methoxy-6*H*-chromeno[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (129d): Under N_2, a solution of TfOH in CH_2Cl_2 (1.0 M, 1.0 mL, 1.0 mmol) was added dropwise to a solution of **148b** (391 mg, 0.65 mmol) in CH_2Cl_2 (15 mL) within 10 min at 0 ºC. After stirring at 0 ºC for 30 min, the mixture was warmed to 23 ºC and stirred for additional 1 h. $NaHCO_3$ (819 mg, 9.75 mmol)

and EtOH (8.0 mL) were added sequentially. Then, the solvent was removed and the residue was dry-loaded on to silica gel and purified by column chromatography on silica gel (*n*-hexane/EtOAc 4/1) to yield **129d** (318 mg, 91%) as a colorless solid.

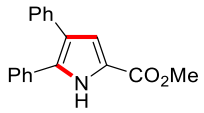
M. p. = 177−178 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.11 (d, J = 7.3 Hz, 1H), 7.35–7.28 (m, 1H), 7.31–7.23 (m, 2H), 7.13–7.03 (m, 4H), 7.02 (s, 1H), 7.02–6.93 (m, 1H), 6.93 (d, J = 7.4 Hz, 1H), 4.69–4.59 (m, 2H), 3.81 (s, 3H), 3.40 (s, 3H), 1.46 (d, J = 6.1 Hz, 3H), 1.41–1.37 (m, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 154.9 (C_q), 151.6 (C_q), 151.2 (C_q), 150.1 (C_q), 148.3 (C_q), 147.2 (C_q), 134.3 (C_q), 128.4 (C_q), 128.3 (C_q), 128.1 (CH), 124.5 (C_q), 124.0 (CH), 123.6 (CH), 123.5 (CH), 122.8 (CH), 118.9 (C_q), 117.9 (C_q), 117.1 (CH), 116.4 (CH), 114.7 (CH), 112.6 (CH), 112.0 (C_q), 110.3 (CH), 108.2 (C_q), 105.5 (CH), 71.3 (CH), 71.1 (CH), 56.0 (CH_3), 54.9 (CH_3), 22.2 (CH_3), 21.8 (CH_3), 21.8 (CH_3), 21.6 (CH_3). **IR** (neat): 2976, 2933, 1701, 1473, 1398, 1259, 1218, 1175, 745 cm^{-1}. **MS** (ESI) *m/z* (relative intensity) 560 (20) [M+Na$^+$], 538 (100) [M+H$^+$], 478 (20), 443 (10), 381 (20). **HR-MS** (ESI) *m/z* calcd for $C_{33}H_{32}NO_6$ [M+H$^+$] 538.2224, found 538.2234.

Synthesis of Lamellarin Analogue 129e



Methyl 2-acetamidoacrylate (**127**) (472 mg, 3.30 mmol), 1,2-diphenylethyne (**59c**) (534 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (46 mg, 2.5 mol %), $AgSbF_6$ (103 mg, 10 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (1.20 g, 6.0 mmol) were placed into a 100 mL sealed tube under a N_2 atmosphere. A solvent mixture of MeOH/DCE (12 mL/6.0 mL) was added *via* cannula. The reaction mixture was stirred at 110 °C for 24 h. At ambient temperature, the reaction mixture was dry-loaded onto silica gel and purified by column chromatography (*n*-hexane/EtOAc

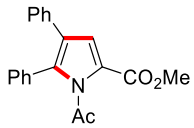
20/1) to afford the desired product **128b** (740 mg, 89%) as a colorless solid and **128b´** (57 mg, 6%) as a pale yellow oil.



Methyl 4,5-diphenyl-1*H*-pyrrole-2-carboxylate (128b):

Clorless solid; **M**. **p**. = 169−170 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 9.55 (s, 1H), 7.44–7.36 (m, 2H), 7.35–7.17 (m, 8H), 7.06 (d, *J* = 2.7 Hz, 1H), 3.83 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 161.8 (C_q), 135.3 (C_q), 133.5 (C_q), 131.8 (C_q), 128.6 (CH), 128.4 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 126.3 (CH), 124.1 (C_q), 122.0 (C_q), 116.8 (CH), 51.6 (CH_3). **IR** (neat): 3258, 1669, 1440, 1226, 1203, 1009, 762, 692, 521 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 278 (20) [M+H$^+$], 277 (100) [M$^+$], 245 (80), 217 (70), 189 (40), 165 (10). **HR-MS** (EI) *m/z* calcd for $C_{18}H_{15}NO_2$ [M$^+$] 277.1103, found 277.1101.

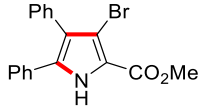
The analytical data are in accordance with those previously reported in the literature.[100, 124f]



Methyl 1-acetyl-4,5-diphenyl-1*H*-pyrrole-2-carboxylate (128b´):

Pale yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.42–7.28 (m, 5H), 7.25–7.11 (m, 6H), 3.88 (s, 3H), 2.32 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 173.7 (C_q), 161.0 (C_q), 134.5 (C_q), 133.8 (C_q), 130.6 (C_q), 130.6 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 126.3 (CH), 124.7 (C_q), 122.9 (C_q), 118.2 (CH), 51.8 (CH_3), 28.8 (CH_3). **IR** (neat): 3392, 1644, 1459, 1440, 1233, 1195, 759, 695 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 320 (5) [M+H$^+$], 319 (10) [M$^+$], 277 (100), 245 (70), 217 (50), 189 (30). **HR-MS** (EI) *m/z* calcd for $C_{20}H_{17}NO_3$ [M$^+$] 319.1208, found 319.1214.

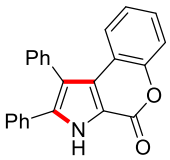
The analytical data are in accordance with those previously reported in the literature.[100]



Methyl 3-bromo-4,5-diphenyl-1*H*-pyrrole-2-carboxylate (144b): To a solution of **128b** (693 mg, 2.50 mmol) in DMF (30 mL), the solution of NBS (449 mg, 2.52 mmol) in DMF (5 mL) was added dropwise within 10 min at 0 °C under a N_2 atmosphere. The reaction mixture was stirred at 0 °C for 1 h. Then, the mixture was diluted with EtOAc (200 mL) and washed with H_2O (3×60 mL) and brine (60 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography over silica gel (*n*-hexane/EtOAc 20/1) to give **144b** (881 mg, 99%) as a colorless solid.

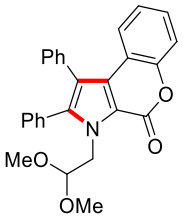
M. **p**. = 190−191 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.53 (s, 1H), 7.37–7.30 (m, 3H), 7.30–7.20 (m, 7H), 3.89 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.9 (C_q), 133.5 (C_q), 133.3 (C_q), 130.8 (C_q), 130.7 (CH),

128.7 (CH), 128.3 (CH), 128.2 (CH), 127.5 (CH), 127.3 (CH), 125.1 (C_q), 119.8 (C_q), 106.0 (C_q), 51.8 (CH_3). **IR** (neat): 3303, 1672, 1461, 1438, 1399, 1288, 1206, 774, 693, 537 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 355 (80) [M^+], 325 (60), 295 (10), 269 (10), 244 (10), 216 (100). **HR-MS** (EI) *m/z* calcd for $C_{18}H_{14}{}^{79}BrNO_2$ [M^+] 355.0208, found 355.0208; $C_{18}H_{14}{}^{81}BrNO_2$ [M^+] 357.0187, found 357.0189.



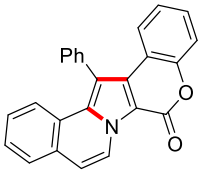
1,2-Diphenylchromeno[3,4-b]pyrrol-4(3*H*)-one (146c): Under N_2, **144b** (712 mg, 2.0 mmol), (2-hydroxyphenyl)boronic acid (**2b**) (414 mg, 3.0 mmol), $Pd_2(dba)_3$ (91.6 mg, 5.0 mol %), dppf (111 mg, 10 mol %) and Na_2CO_3 (1.40 g, 13.2 mmol) were placed into a 100 mL sealed tube. A solvent mixture of DME/H_2O (30 mL/2.4 mL) was added *via* cannula. The reaction mixture was kept in the dark and stirred at 110 °C for 36 h. After cooling to ambient temperature, the mixture was evaporated, and the residue was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (4×30 mL). The extract was washed with brine (2×30 mL), dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel (*n*-hexane/EtOAc 3/1) to give **146c** as a colorless solid (526 mg, 78%).

M. p. = 273−274 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 10.27 (s, 1H), 7.51–7.38 (m, 6H), 7.37–7.25 (m, 7H), 7.01 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 155.7 (C_q), 151.5 (C_q), 139.0 (C_q), 134.3 (C_q), 131.0 (CH), 130.6 (C_q), 129.0 (CH), 128.8 (CH), 128.6 (CH), 127.9 (CH), 127.9 (C_q), 127.7 (CH), 127.7 (CH), 124.0 (CH), 123.4 (CH), 119.1 (C_q), 118.3 (C_q), 117.5 (CH), 116.6 (C_q). **IR** (neat): 3231, 1692, 1426, 1300, 1131, 977, 749, 703, 535 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 338 (80) [M+H^+], 337 (100) [M^+], 322 (10), 308 (10), 291 (10), 280 (10). **HR-MS** (EI) *m/z* calcd for $C_{23}H_{15}NO_2$ [M^+] 337.1103, found 337.1097.



3-(2,2-Dimethoxyethyl)-1,2-diphenylchromeno[3,4-b]pyrrol-4(3*H*)-one (148c): Under N_2, **146c** (337 mg, 1.0 mmol) and Cs_2CO_3 (2.11 g, 6.5 mmol) were placed into a 100 mL sealed tube. 2-Bromo-1,1-dimethoxyethane (**147**) (1.11 g, 6.6 mmol) and DMF (15 mL) were added *via* cannula. The reaction mixture was stirred at 110 °C for 36 h. At ambient temperature, the mixture was diluted with EtOAc (200 mL) and washed with H_2O (3×50 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography over silica gel (*n*-hexane/EtOAc 6/1) to give **148c** (264 mg, 62%) as a colorless solid.

M. p. = 146−148 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.38 (ddd, *J* = 8.3, 1.4, 0.5 Hz, 1H), 7.36–7.30 (m, 2H), 7.29–7.22 (m, 10H), 6.97 (ddd, *J* = 7.9, 7.2, 1.3 Hz, 1H), 4.75 (t, *J* = 5.5 Hz, 1H), 4.51 (d, *J* = 5.5 Hz, 2H), 3.27 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 155.4 (C_q), 151.4 (C_q), 144.2 (C_q), 134.2 (C_q), 131.3 (CH), 131.0 (CH), 129.8 (C_q), 128.6 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.3 (CH), 127.1 (C_q), 123.7 (CH), 123.5 (CH), 120.0 (C_q), 118.1 (C_q), 117.1 (CH), 115.8 (C_q), 104.3 (CH), 55.3 (CH_3), 47.9 (CH_2). **IR** (neat): 3060, 2927, 2838, 1713, 1607, 1454, 1074, 1048, 706 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 425 (20) [M^+], 410 (5), 394 (10), 364 (20), 337 (10), 320 (10), 75 (100). **HR-MS** (EI) *m/z* calcd for $C_{27}H_{23}NO_4$ [M^+] 425.1627, found 425.1636.

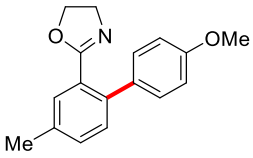


14-Phenyl-6*H*-chromeno[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (129e): Following a modified procedure,[11a] **148c** (44 mg, 0.10 mmol) was placed into a 25 mL sealed tube under a N_2 atmosphere. A solvent mixture of $CF_3COOH/(CF_3CO)_2O$ (3.0 mL/1.0 mL) was added *via* cannula. The mixture was stirred at 75 °C for 48 h. At ambient temperature, the excess anhydride and acid were removed by evaporation. NEt_3 (0.50 mL) was added and this mixture was dry-loaded onto silica gel and purified by column chromatography over silica gel (*n*-hexane/EtOAc 20/1) to give **129e** (24 mg, 64%) as a colorless solid.

M. p. > 300 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 9.36 (d, *J* = 7.4 Hz, 1H), 7.72–7.69 (m, 1H), 7.67–7.62 (m, 3H), 7.59–7.54 (m, 2H), 7.53–7.42 (m, 3H), 7.34 (ddd, *J* = 8.4, 7.1, 1.7 Hz, 1H), 7.25 (ddd, *J* = 8.5, 7.3, 1.3 Hz, 1H), 7.14 (d, *J* = 7.4 Hz, 1H), 7.11 (ddd, *J* = 7.9, 1.7, 0.5 Hz, 1H), 7.00 (ddd, *J* = 8.1, 7.1, 1.4 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 155.3 (C_q), 151.7 (C_q), 135.6 (C_q), 134.1 (C_q), 131.0 (CH), 129.9 (CH), 129.7 (C_q), 128.7 (CH), 128.4 (CH), 128.2 (CH), 127.5 (CH), 127.3 (CH), 125.0 (C_q), 124.5 (CH), 124.4 (CH), 124.1 (CH), 123.9 (CH), 117.9 (C_q), 117.4 (CH), 114.3 (C_q), 113.5 (CH), 109.4 (C_q). **IR** (neat): 3059, 3046, 1426, 1701, 1409, 1368, 1178, 1048, 788 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 362 (30) [$M+H^+$], 361 (100) [M^+], 337 (10), 315 (10), 304 (10), 276 (5). **HR-MS** (EI) *m/z* calcd for $C_{25}H_{15}NO_2$ [M^+] 361.1103, found 361.1092.

The analytical data are in accordance with those previously reported in the literature.[122b, 122g]

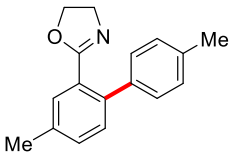
5.3.4 Cobalt-Catalyzed C–H Functionalizations by Imidate Assistance with Aryl and Alkyl Chlorides



2-(4'-Methoxy-4-methyl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (131aa): The general procedure **D** was followed using oxazoline **130a** (80.6 mg, 0.50 mmol) and aryl chloride **8a** (92.7 mg, 0.65 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131aa** (105.6 mg, 79%) as a colorless oil.

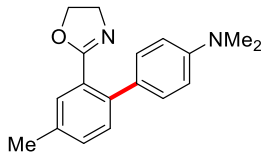
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.55 (s, 1H), 7.27 (d, J = 8.7 Hz, 2H), 7.26–7.22 (m, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.12 (t, J = 9.6 Hz, 2H), 3.90 (t, J = 9.6 Hz, 2H), 3.82 (s, 3H), 2.37 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.3 (C_q), 158.6 (C_q), 138.5 (C_q), 136.4 (C_q), 133.6 (C_q), 131.2 (CH), 130.6 (CH), 130.1 (CH), 129.3 (CH), 127.1 (C_q), 113.4 (CH), 67.8 (CH_2), 55.2 (CH_3), 54.9 (CH_2), 20.9 (CH_3). **IR** (ATR): 2934, 2835, 1647, 1608, 1487, 1424, 1176, 819, 538 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 268 (10) [M+H$^+$], 267 (40) [M$^+$], 266 (100), 251 (15), 222 (20). **HR-MS** (ESI) *m/z* calcd for $C_{17}H_{18}NO_2$ [M+H$^+$] 268.1332, found 268.1338.

The analytical data are in accordance with those previously reported in the literature.[28]



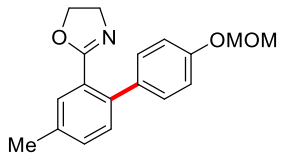
2-(4,4'-Dimethyl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (131ab): The general procedure **D** was followed using oxazoline **130a** (80.6 mg, 0.50 mmol), aryl chloride **8b** (82.3 mg, 0.65 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 8:1) yielded **131ab** (89.2 mg, 71%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.58–7.54 (m, 1H), 7.29–7.25 (m, 2H), 7.24 (d, J = 7.8 Hz, 2H), 7.16 (d, J = 7.8 Hz, 2H), 4.12 (td, J = 9.5, 0.8 Hz, 2H), 3.90 (td, J = 9.5, 0.8 Hz, 2H), 2.38 (s, 3H), 2.36 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.3 (C_q), 138.8 (C_q), 138.2 (C_q), 136.6 (C_q), 136.5 (C_q), 131.2 (CH), 130.6 (CH), 130.2 (CH), 128.6 (CH), 128.1 (CH), 127.1 (C_q), 67.8 (CH_2), 55.0 (CH_2), 21.2 (CH_3), 20.9 (CH_3). **IR** (ATR): 2921, 2874, 1647, 1325, 1198, 975 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 252 (5) [M+H$^+$], 251 (40) [M$^+$], 250 (100), 206 (40), 191 (15). **HR-MS** (EI) *m/z* calcd for $C_{17}H_{16}NO$ [M-H]$^+$ 250.1232, found 250.1227.



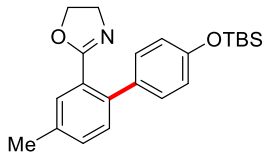
2'-(4,5-Dihydrooxazol-2-yl)-N,N,4'-trimethyl-[1,1'-biphenyl]-4-amine (131ac): The general procedure **D** was followed using oxazoline **130a** (80.6 mg, 0.50 mmol), aryl chloride **8c** (101.1 mg, 0.65 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131ac** (103.7 mg, 74%) as a colorless solid.

M. p. = 126−127 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.52 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.28–7.22 (m, 4H), 6.73 (d, *J* = 8.9 Hz 2H), 4.15 (td, *J* = 9.5, 0.8 Hz, 2H), 3.92 (td, *J* = 9.5, 0.8 Hz, 2H), 2.96 (s, 6H), 2.36 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.8 (C_q), 149.5 (C_q), 138.9 (C_q), 135.7 (C_q), 131.1 (CH), 130.6 (CH), 130.0 (CH), 129.1 (C_q), 128.9 (CH), 126.9 (C_q), 112.1 (CH), 67.9 (CH_2), 54.9 (CH_2), 40.6 (CH_3), 20.9 (CH_3). **IR** (ATR): 2876, 1651, 1608, 1530, 1488, 1358, 1193, 945, 808 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 281 (5) [M+H$^+$], 280 (50) [M$^+$], 279 (100), 263 (10), 235 (30). **HR-MS** (EI) *m/z* calcd for $C_{18}H_{19}N_2O$ [M-H]$^+$ 279.1497, found 279.1487.



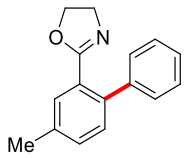
2-{4'[-Methoxymethoxy]-4-methyl-[1,1'-biphenyl]-2-yl}-4,5-dihydrooxazole (131ad): The general procedure **D** was followed using oxazoline **130a** (80.6 mg, 0.50 mmol), aryl chloride **8d** (112.2 mg, 0.65 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131ad** (107.0 mg, 72%) as a colorless solid.

M. p. = 63−64 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.55 (d, *J* = 1.8 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.25–7.22 (m, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 5.18 (s, 2H), 4.12 (td, *J* = 9.5, 0.8 Hz, 2H), 3.90 (td, *J* = 9.5, 0.8 Hz, 2H), 3.48 (s, 3H), 2.37 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.2 (C_q), 156.3 (C_q), 138.3 (C_q), 136.5 (C_q), 134.8 (C_q), 131.1 (CH), 130.6 (CH), 130.1 (CH), 129.3 (CH), 127.1 (C_q), 115.7 (CH), 94.5 (CH_2), 67.8 (CH_2), 56.0 (CH_3), 54.9 (CH_2), 20.9 (CH_3). **IR** (ATR): 2899, 1644, 1606, 1515, 1483, 1231, 1196, 1076, 827 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 298 (5) [M+H$^+$], 297 (20) [M$^+$], 296 (100), 266 (10), 252 (40). **HR-MS** (EI) *m/z* calcd for $C_{18}H_{18}NO_3$ [M-H]$^+$ 296.1287, found 296.1279.



2-(4'-[{*tert*-Butyldimethylsilyl}oxy]-4-methyl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (131ae): The general procedure **D** was followed using oxazoline **130a** (80.6 mg, 0.50 mmol), aryl chloride **8e** (157.8 mg, 0.65 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131ae** (104.7 mg, 57%) as a colorless solid.

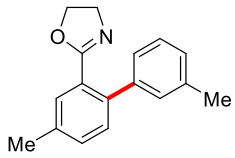
M. p. = 97−98 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.53 (dd, J = 1.4, 0.7 Hz, 1H), 7.31–7.23 (m, 2H), 7.20 (d, J = 8.7 Hz, 2H),6.82 (d, J = 8.7 Hz, 2H), 4.09 (td, J = 9.4, 0.9 Hz, 2H), 3.89 (td, J = 9.4, 0.9 Hz, 2H), 2.37 (s, 3H), 0.98 (s, 9H), 0.20 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.4 (C_q), 154.7 (C_q), 138.6 (C_q), 136.4 (C_q), 134.2 (C_q), 131.1 (CH), 130.5 (CH), 130.0 (CH), 129.2 (CH), 127.2 (C_q), 119.5 (CH), 67.7 (CH_2), 54.9 (CH_2), 25.8 (CH_3), 20.9 (CH_3), 18.3 (C_q), -4.3 (CH_3). **IR** (ATR): 2951, 2928, 1605, 1519, 1257, 913, 830, 776 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 368 (5) [M+H$^+$], 367 (25) [M$^+$], 366 (100), 310 (10), 266 (10). **HR-MS** (EI) *m/z* calcd for $C_{22}H_{28}NO_2Si$ [M-H]$^+$ 366.1889, found 366.1880.



2-(4-Methyl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (130af): The general procedure **D** was followed using oxazoline **130a** (80.6 mg, 0.50 mmol), aryl chloride **8f** (73.2 mg, 0.65 mmol) and ICyHCl (**149i)** (6.8 mg, 5.0 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131af** (79.5 mg, 67%) as a colorless oil.

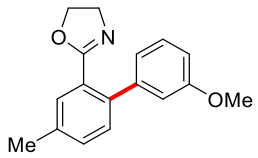
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.61–7.56 (m, 1H), 7.39–7.31 (m, 4H), 7.33–7.23 (m, 3H), 4.09 (td, J = 9.4, 0.9 Hz, 2H), 3.89 (td, J = 9.5, 0.9 Hz, 2H), 2.39 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.1 (C_q), 141.1 (C_q), 138.9 (C_q), 136.8 (C_q), 131.2 (CH), 130.6 (CH), 130.2 (CH), 128.2 (CH), 127.8 (CH), 127.2 (C_q), 126.8 (CH), 67.8 (CH_2), 55.0 (CH_2), 20.9 (CH_3). **IR** (ATR): 3025, 2877, 1647, 1480, 1192, 1081, 976, 700, 534 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 238 (5) [M+H$^+$], 237 (40) [M$^+$], 236 (100), 192 (50), 178 (20). **HR-MS** (EI) *m/z* calcd for $C_{16}H_{14}NO$ [M-H]$^+$ 236.1075, found 236.1077.

The analytical data are in accordance with those previously reported in the literature.[20e]



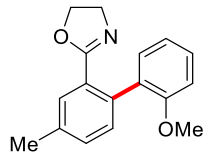
2-(3',4-Dimethyl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (131ag): The general procedure **D** was followed using oxazoline **130a** (80.6 mg, 0.50 mmol), aryl chloride **8g** (82.3 mg, 0.65 mmol) and ICyHCl (**149i)** (6.8 mg, 5.0 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131ag** (96.7 mg, 77%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.56 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.29–7.26 (m, 2H), 7.26–7.21 (m, 1H), 7.18 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.16–7.13 (m, 1H), 7.11 (ddd, *J* = 7.5, 1.6, 0.8 Hz, 1H), 4.10 (td, *J* = 9.4, 0.9 Hz, 2H), 3.90 (td, *J* = 9.4, 0.9 Hz, 2H), 2.38 (s, 3H), 2.37 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.4 (C_q), 141.1 (C_q), 139.0 (C_q), 137.5 (C_q), 136.8 (C_q), 131.2 (CH), 130.6 (CH), 130.2 (CH), 129.0 (CH), 127.8 (CH), 127.7 (CH), 127.2 (C_q), 125.4 (CH), 67.8 (CH_2), 54.9 (CH_2), 21.5 (CH_3), 20.8 (CH_3). **IR** (ATR): 2922, 2876, 1648, 1348, 1270, 1196, 976, 786 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 251 (20) [M^+], 250 (100) [M-H]$^+$, 236 (10), 206 (30), 191 (10). **HR-MS** (EI) *m/z* calcd for $C_{17}H_{16}NO$ [M-H]$^+$ 250.1232, found 250.1235.



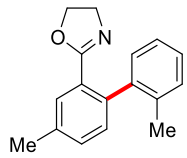
2-(3'-Methoxy-4-methyl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (131ah): The general procedure **D** was followed using oxazoline **130a** (80.6 mg, 0.50 mmol), aryl chloride **8h** (92.7 mg, 0.65 mmol) and ICyHCl (**149i)** (6.8 mg, 5.0 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131ah** (96.2 mg, 72%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.30–7.25 (m, 3H), 6.95–6.89 (m, 2H), 6.85 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 4.11 (td, *J* = 9.6, 1.0 Hz, 2H), 3.90 (td, *J* = 9.6, 1.0 Hz, 2H), 3.80 (s, 3H), 2.38 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.3 (C_q), 159.3 (C_q), 142.6 (C_q), 138.8 (C_q), 137.0 (C_q), 131.2 (CH), 130.6 (CH), 130.2 (CH), 128.9 (CH), 127.3 (C_q), 120.9 (CH), 113.8 (CH), 112.7 (CH), 67.9 (CH_2), 55.2 (CH_3), 55.0 (CH_2), 20.8 (CH_3). **IR** (ATR): 2936, 1649, 1581, 1476, 1211, 1046, 948, 782, 698 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 267 (30) [M^+], 266 (100) [M-H]$^+$, 251 (10), 236 (15), 222 (20). **HR-MS** (EI) *m/z* calcd for $C_{17}H_{16}NO_2$ [M-H$^+$] 266.1181, found 266.1176.



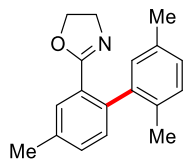
2-(2'-Methoxy-4-methyl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (131ai): The general procedure **D** was followed using oxazoline **130a** (80.6 mg, 0.50 mmol) and aryl chloride **8i** (92.7 mg, 0.65 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131ai** (102.9 mg, 77%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.67 (dd, *J* = 1.9, 0.6 Hz, 1H), 7.31–7.26 (m, 2H), 7.21 (d, *J* = 7.4 Hz, 1H), 7.20 (d, *J* = 7.4 Hz, 1H), 6.99 (ddd, *J* = 7.4, 1.1, 1.1 Hz, 1H), 6.87 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.09 (dt, *J* = 9.5, 0.8 Hz, 2H), 3.85 (t, *J* = 9.5 Hz, 2H), 3.71 (s, 3H), 2.38 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.0 (C_q), 156.3 (C_q), 136.7 (C_q), 135.3 (C_q), 131.1 (CH), 131.1 (CH), 130.6 (C_q), 130.1 (CH), 129.9 (CH), 128.4 (CH), 128.0 (C_q), 120.4 (CH), 110.1 (CH), 67.5 (CH_2), 55.3 (CH_3), 54.8 (CH_2), 21.0 (CH_3). **IR** (ATR): 2934, 2833, 1645, 1483, 1242, 1050, 1003, 750 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 266 (5) $[M-H]^+$, 250 (5), 236 (100), 192 (30), 165 (20). **HR-MS** (ESI) *m/z* calcd for $C_{17}H_{18}NO_2$ $[M+H^+]$ 268.1332, found 268.1334.



2-(2',4-Dimethyl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (131aj): The general procedure **D** was followed using oxazoline **130a** (80.5 mg, 0.50 mmol), aryl chloride **8j** (82.3 mg, 0.65 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131aj** (100.5 mg, 80%) as a colorless oil.

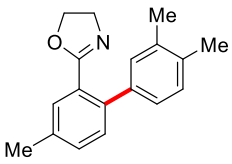
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 1.9 Hz, 1H), 7.27 (ddd, *J* = 7.8, 1.9, 0.8 Hz, 1H), 7.24–7.12 (m, 3H), 7.13–7.07 (m, 2H), 4.10–3.92 (m, 2H), 3.81 (t, *J* = 9.0 Hz, 2H), 2.40 (s, 3H), 2.08 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 165.7 (C_q), 141.2 (C_q), 138.7 (C_q), 136.6 (C_q), 135.6 (C_q), 130.9 (CH), 130.4 (CH), 130.1 (CH), 129.2 (CH), 128.9 (CH), 127.5 (C_q), 126.9 (CH), 124.9 (CH), 67.6 (CH_2), 54.8 (CH_2), 21.0 (CH_3), 20.1 (CH_3). **IR** (ATR): 3019, 2923, 2875, 1645, 1479, 1191, 1080, 977, 755 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 250 (5) $[M-H]^+$, 237 (20), 236 (100), 192 (30), 165 (20). **HR-MS** (ESI) *m/z* calcd for $C_{17}H_{18}NO$ $[M+H^+]$ 252.1383, found 252.1386.



2-(2',4,5'-Trimethyl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (131ak): The general procedure **D** was followed using oxazoline **130a** (80.5 mg, 0.50 mmol) and aryl chloride **8k** (91.4 mg, 0.65 mmol). Purification

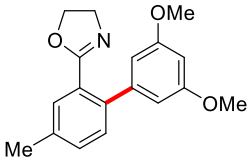
by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131ak** (98.2 mg, 74%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.68 (d, *J* = 1.8 Hz, 1H), 7.26 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 7.01 (dd, *J* = 7.7, 1.8 Hz, 1H), 6.93 (s, 1H), 4.10–3.96 (m, 2H), 3.82 (t, *J* = 9.6 Hz, 2H), 2.39 (s, 3H), 2.30 (s, 3H), 2.04 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 165.8 (C_q), 141.0 (C_q), 138.9 (C_q), 136.5 (C_q), 134.2 (C_q), 132.5 (C_q), 130.9 (CH), 130.5 (CH), 130.0 (CH), 129.6 (CH), 129.1 (CH), 127.6 (CH), 127.5 (C_q), 67.6 (CH_2), 54.8 (CH_2), 21.0 (CH_3), 21.0 (CH_3), 19.6 (CH_3). **IR** (ATR): 2920, 1645, 1347, 1195, 1080, 977, 826 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 264 (5) $[M-H]^+$, 251 (20), 250 (100), 206 (30), 191 (20), 178 (20). **HR-MS** (ESI) *m/z* calcd for $C_{18}H_{20}NO$ $[M+H^+]$ 266.1539, found 266.1543.



2-(3',4,4'-Trimethyl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (131al): The general procedure **D** was followed using oxazoline **130a** (80.6 mg, 0.50 mmol) and aryl chloride **8l** (91.4 mg, 0.65 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131al** (86.2 mg, 65%) as a colorless oil.

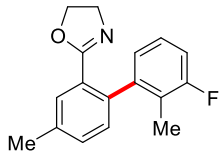
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 0.5 Hz, 1H), 7.28 (d, *J* = 8.3 Hz, 1H), 7.16–6.99 (m, 3H), 6.95 (s, 1H), 4.15–3.95 (m, 2H), 3.84 (t, *J* = 9.0 Hz, 2H), 2.41 (s, 3H), 2.32 (s, 3H), 2.05 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 165.9 (C_q), 141.1 (C_q), 139.0 (C_q), 136.6 (C_q), 134.3 (C_q), 132.5 (C_q), 131.0 (CH), 130.6 (CH), 130.1 (CH), 129.7 (CH), 129.2 (CH), 127.6 (CH), 127.6 (C_q), 67.6 (CH_2), 54.8 (CH_2), 20.9 (CH_3), 20.9 (CH_3), 19.5 (CH_3). **IR** (ATR): 2920, 1645, 1489, 1348, 1196, 1080, 977, 826 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 264 (5) $[M-H]^+$, 251 (20), 250 (100), 206 (30), 191 (10), 179 (20). **HR-MS** (ESI) *m/z* calcd for $C_{18}H_{20}NO$ $[M+H^+]$ 266.1539, found 266.1542.



2-(3',5'-Dimethoxy-4-methyl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (131am): The general procedure **D** was followed using oxazoline **130a** (80.6 mg, 0.50 mmol), aryl chloride **8m** (112.2 mg, 0.65 mmol) and ICyHCl (**149i)** (6.8 mg, 5.0 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131am** (98.1 mg, 66%) as a colorless oil.

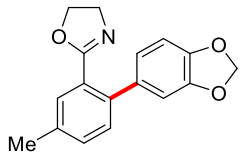
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.56 (s, 1H), 7.29 (d, *J* = 1.2 Hz, 2H), 6.54 (dd, *J* = 2.2, 2.2 Hz, 2H), 6.43 (t, *J* = 2.2 Hz, 1H), 4.16 (td, *J* = 9.2, 1.3 Hz, 2H), 3.93 (td, *J* = 9.2, 1.3 Hz, 2H), 3.79 (s, 6H), 2.39 (s, 3H). **^{13}C**

NMR (75 MHz, $CDCl_3$) δ = 166.3 (C_q), 160.3 (C_q), 143.2 (C_q), 138.8 (C_q), 137.1 (C_q), 131.2 (CH), 130.6 (CH), 130.0 (CH), 127.3 (C_q), 106.4 (CH), 99.4 (CH), 67.9 (CH_2), 55.3 (CH_3), 55.0 (CH_2), 20.8 (CH_3). **IR** (ATR): 2935, 2836, 1590, 1453, 1422, 1201, 1150, 1062, 818, 690 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 297 (30) [M^+], 296 (100) [M-H]$^+$, 282 (20), 266 (100), 252 (30), 238 (10), 210 (10). **HR-MS** (ESI) *m/z* calcd for $C_{18}H_{20}NO_3$ [M+H$^+$] 298.1438, found 298.1440.



2-(3'-Fluoro-2',4-dimethyl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (131an): The general procedure **D** was followed using oxazoline **130a** (80.6 mg, 0.50 mmol), aryl chloride **8n** (94.0 mg, 0.65 mmol) and ICyHCl (**149i)** (6.8 mg, 5.0 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131an** (68.7 mg, 51%) as a colorless oil.

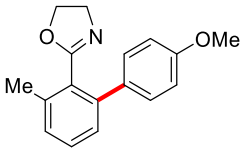
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.70 (dd, *J* = 1.3, 0.7 Hz, 1H), 7.27 (ddd, *J* = 7.8, 1.9, 0.7 Hz, 1H), 7.16–7.05 (m, 2H), 6.96 (ddd, *J* = 9.6, 8.2, 1.3 Hz, 1H), 6.89 (dd, *J* = 7.5, 1.3 Hz, 1H), 4.13–3.93 (m, 2H), 3.82 (t, *J* = 9.3 Hz, 2H), 2.40 (s, 3H), 1.98 (d, *J* = 2.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 165.5 (C_q), 161.0 (d, $^1J_{C\text{-}F}$ = 243.0 Hz, C_q), 143.7 (d, $^3J_{C\text{-}F}$ = 4.7 Hz, C_q), 137.4 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, C_q), 137.2 (C_q), 131.1 (CH), 130.5 (CH), 130.2 (CH), 127.6 (C_q), 125.8 (d, $^3J_{C\text{-}F}$ = 9.1 Hz, CH), 124.7 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, CH), 123.2 (d, $^2J_{C\text{-}F}$ = 16.8 Hz, C_q), 113.5 (d, $^2J_{C\text{-}F}$ = 23.0 Hz, CH), 67.7 (CH_2), 54.9 (CH_2), 20.9 (CH_3), 11.8 (d, $^3J_{C\text{-}F}$ = 4.7 Hz, CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -117.1 (m). IR (ATR): 2928, 1648, 1457, 1236, 1111, 1071, 977, 786 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 268 (5) [M-H]$^+$, 255 (20), 254 (100), 210 (30), 196 (10), 183 (20). **HR-MS** (EI) *m/z* calcd for $C_{17}H_{15}FNO$ [M-H]$^+$ 268.1138, found 268.1141.



2-(2-{Benzo[*d*][1,3]dioxol-5-yl}-5-methylphenyl)-4,5-dihydrooxazole (3ao): The general procedure **D** was followed using oxazoline **130a** (80.6 mg, 0.50 mmol) and aryl chloride **8o** (101.8 mg, 0.65 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1) yielded **131ao** (59.1 mg, 42%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (dd, *J* = 1.6, 0.9 Hz, 1H), 7.27–7.23 (m, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 6.84 (dd, *J* = 1.1 Hz, 1.1 Hz, 1H), 6.80 (d, *J* = 1.1 Hz, 2H), 5.96 (s, 2H), 4.15 (td, *J* = 9.5, 0.9 Hz, 2H), 3.91 (td, *J* = 9.5, 0.9 Hz, 2H), 2.37 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.2 (C_q), 147.3 (C_q), 146.7 (C_q), 138.5 (C_q), 136.7 (C_q), 135.2 (C_q), 131.2 (CH), 130.7 (CH), 130.2 (CH), 127.2 (C_q), 121.7 (CH), 108.9 (CH), 107.9 (CH), 101.0 (CH_2), 67.8 (CH_2), 54.9 (CH_2), 20.8 (CH_3). **IR** (ATR): 2878, 1648, 1475, 1336, 1218, 1034, 933,

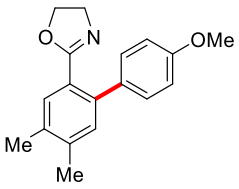
806, 537 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 281 (30) [M^+], 280 (100) [M-H]$^+$, 237 (5), 236 (30), 223 (10), 152 (20). **HR-MS** (ESI) *m/z* calcd for $C_{17}H_{15}NO_3Na$ [M+Na^+] 304.0944, found 304.0943.



2-(4'-Methoxy-3-methyl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (131ba): The general procedure **D** was followed using oxazoline **130b** (80.6 mg, 0.50 mmol) and aryl chloride **8a** (92.7 mg, 0.65 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 8:1) yielded **131ba** (97.6 mg, 73%) as a colorless oil.

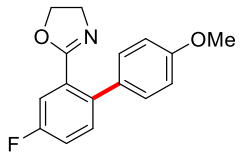
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.35–7.31 (m, 2H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 6.89 (d, *J* = 7.7 Hz, 2H), 4.14 (t, *J* = 9.5 Hz, 2H), 3.86 (t, *J* = 9.5 Hz, 2H), 3.81 (s, 3H), 2.39 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 164.4 (C_q), 158.7 (C_q), 141.5 (C_q), 137.3 (C_q), 133.6 (C_q), 129.4 (CH), 129.3 (CH), 128.5 (CH), 128.0 (C_q), 127.1 (CH), 113.4 (CH), 67.2 (CH_2), 55.2 (CH_3), 55.1 (CH_2), 19.9 (CH_3). **IR** (ATR): 2957, 1666, 1515, 1041 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 267 (30) [M^+], 266 (100) [M-H]$^+$, 251 (10), 222 (15), 195 (10), 165 (10). **HR-MS** (ESI) *m/z* calcd for $C_{17}H_{18}NO_2$ [M+H^+] 268.1332, found 268.1335.

The analytical data are in accordance with those previously reported in the literature.[20e]



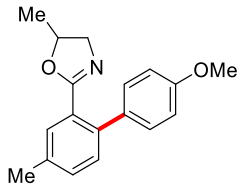
2-(4'-Methoxy-4,5-dimethyl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (131ca): The general procedure **D** was followed using oxazoline **1c** (87.6 mg, 0.50 mmol) and aryl chloride **8a** (92.7 mg, 0.65 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131ca** (101.3 mg, 72%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.53 (s, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.12 (s, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.10 (td, *J* = 9.6, 1.3 Hz, 2H), 3.88 (td, *J* = 9.6, 1.3 Hz, 2H), 3.81 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 166.3 (C_q), 158.6 (C_q), 139.2 (C_q), 138.8 (C_q), 135.1 (C_q), 133.7 (C_q), 131.5 (CH), 131.2 (CH), 129.3 (CH), 124.5 (C_q), 113.3 (CH), 67.6 (CH_2), 55.1 (CH_3), 54.8 (CH_2), 19.6 (CH_3), 19.0 (CH_3). **IR** (ATR): 2936, 2834, 1646, 1608, 1490, 1242, 1176, 1031, 830 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 281 (20) [M^+], 280 (100) [M-H]$^+$, 265 (10), 236 (20), 223 (15), 165 (15). **HR-MS** (EI) *m/z* calcd for $C_{18}H_{18}NO_2$ [M-H]$^+$ 280.1338, found 280.1344.



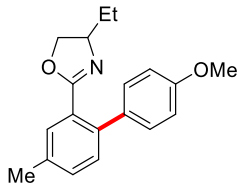
2-(4-Fluoro-4'-methoxy-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (131da): The general procedure **D** was followed using oxazoline **130d** (82.6 mg, 0.50 mmol) and aryl chloride **8a** (92.7 mg, 0.65 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 8:1) yielded **131da** (95.0 mg, 70%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.52 (d, J = 7.1 Hz, 1H), 7.37–7.13 (m, 4H), 6.92 (d, J = 8.8 Hz, 2H), 4.07 (t, J = 9.4 Hz, 2H), 3.85 (t, J = 9.4 Hz, 2H), 3.81 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 164.9 (d, $^{4}J_{C\text{-}F}$ = 3.5 Hz, C_q), 159.7 (d, $^{1}J_{C\text{-}F}$ = 245.2 Hz, C_q), 159.1 (C_q), 130.5 (d, $^{5}J_{C\text{-}F}$ = 1.6 Hz, CH), 130.4 (d, $^{4}J_{C\text{-}F}$ = 3.4 Hz, C_q), 129.1 (d, $^{3}J_{C\text{-}F}$ = 17.3 Hz, C_q), 128.3 (d, $^{2}J_{C\text{-}F}$ = 8.8 Hz, CH), 126.1 (C_q), 125.6 (d, $^{3}J_{C\text{-}F}$ = 3.6 Hz, CH), 117.8 (d, $^{2}J_{C\text{-}F}$ = 23.6 Hz, CH), 113.4 (CH), 67.9 (CH_2), 55.2 (CH_3), 54.9 (CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -115.40 (dd, J = 9.4, 5.1 Hz). **IR** (ATR): 2935, 2836, 1517, 1452, 1242, 1177, 1035, 978, 830, 747 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 271 (20) [M^+], 270 (100) [M-H]$^+$, 255 (10), 226 (20), 170 (15), 157 (10). **HR-MS** (ESI) *m/z* calcd for $C_{16}H_{15}FNO_2$ [M+H$^+$] 272.1081, found 272.1084.



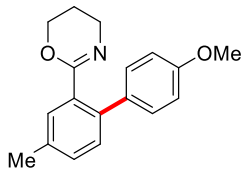
2-(4'-Methoxy-4-methyl-[1,1'-biphenyl]-2-yl)-5-methyl-4,5-dihydrooxazole (131ea): The general procedure was followed using oxazoline **130e** (87.6 mg, 0.50 mmol) and aryl chloride **8a** (92.7 mg, 0.65 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131ea** (113.9 mg, 81%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.53 (d, J = 0.8 Hz, 1H), 7.33–7.19 (m, 4H), 6.89 (d, J = 8.8 Hz, 2H), 4.56 (tdd, J = 9.5, 7.4, 6.2 Hz, 1H), 3.99 (dd, J = 14.3, 9.5 Hz, 1H), 3.80 (s, 3H), 3.45 (dd, J = 14.3, 7.4 Hz, 1H), 2.37 (s, 3H), 1.14 (d, J = 6.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 165.4 (C_q), 158.6 (C_q), 138.4 (C_q), 136.3 (C_q), 133.5 (C_q), 130.9 (CH), 130.4 (CH), 130.1 (CH), 129.5 (CH), 127.5 (C_q), 113.2 (CH), 76.1 (CH), 61.6 (CH_2), 55.1 (CH_3), 20.7 (CH_3), 20.7 (CH_3). **IR** (ATR): 2931, 1609, 1519, 1243, 1176, 1035, 819, 540 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 281 (30) [M^+], 280 (100) [M-H]$^+$, 239 (30), 222 (20), 209 (10), 196 (10). **HR-MS** (EI) *m/z* calcd for $C_{18}H_{18}NO_2$ [M-H$^+$] 280.1338, found 280.1341.



4-Ethyl-2-(4'-methoxy-4-methyl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (131fa): The general procedure **D** was followed using oxazoline **130f** (94.6 mg, 0.50 mmol), aryl chloride **8a** (92.7 mg, 0.65 mmol) and ICyHCl (**149i)** (6.8 mg, 5.0 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131fa** (94.5 mg, 64%) as a colorless oil.

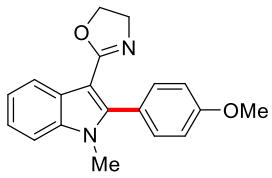
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.54 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.33–7.19 (m, 4H), 6.89 (d, *J* = 8.8 Hz 2H), 4.23–4.01 (m, 2H), 3.82 (s, 3H), 3.74 (d, *J* = 7.3 Hz, 1H), 2.37 (s, 3H), 1.79–1.42 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 165.5 (C_q), 158.7 (C_q), 138.4 (C_q), 136.4 (C_q), 133.6 (C_q), 131.1 (CH), 130.7 (CH), 130.1 (CH), 129.4 (CH), 127.4 (C_q), 113.3 (CH), 72.4 (CH_2), 67.8 (CH), 55.2 (CH_3), 28.3 (CH_2), 20.8 (CH_3), 10.0 (CH_3). **IR** (ATR): 2961, 2835, 1609, 1487, 1243, 1176, 1036, 819, 542 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 295 (30) [M^+], 294 (100) [M-H]$^+$, 280 (10), 240 (20), 225 (10), 209 (10). **HR-MS** (EI) *m/z* calcd for $C_{19}H_{20}NO_2$ [M-H]$^+$ 294.1494, found 294.1489.



2-(4'-Methoxy-4-methyl-[1,1'-biphenyl]-2-yl)-5,6-dihydro-4H-1,3-oxazine (131ga): The general procedure **D** was followed using oxazine **130g** (87.6 mg, 0.50 mmol) and aryl chloride **8a** (92.7 mg, 0.65 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **131ga** (67.5 mg, 48%) as a colorless solid.

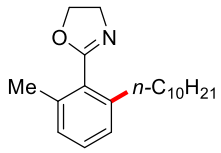
M. p. = 113−114 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.37–7.31 (m, 3H), 7.19 (d, *J* = 1.0 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.90 (t, *J* = 5.5 Hz, 2H), 3.82 (s, 3H), 3.48 (t, *J* = 5.9 Hz, 2H), 2.35 (s, 3H), 1.82 (tt, *J* = 11.5, 5.9 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 158.9 (C_q), 158.5 (C_q), 137.3 (C_q), 136.4 (C_q), 134.2 (C_q), 134.2 (C_q), 130.1 (CH), 129.8 (CH), 129.8 (CH), 129.3 (CH), 113.4 (CH), 65.0 (CH_2), 55.2 (CH_3), 42.8 (CH_2), 21.6 (CH_2), 20.8 (CH_3).

IR (ATR): 3002, 2932, 2860, 1659, 1294, 1099, 823, 548 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 281 (30) [M^+], 280 (100) [M-H]$^+$, 252 (40), 222 (40), 209 (10), 181 (10). **HR-MS** (ESI) *m/z* calcd for $C_{18}H_{20}NO_2$ [M+H$^+$] 282.1489, found 282.1490.



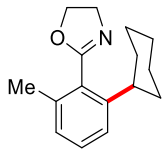
2-[2-(4-Methoxyphenyl)-1-methyl-1*H*-indol-3-yl]-4,5-dihydrooxazole (131ha): The general procedure **D** was followed using oxazoline **130h** (100.1 mg, 0.50 mmol) and aryl chloride **8a** (92.7 mg, 0.65 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1) yielded **131ha** (61.3 mg, 40%) as a colorless solid.

M. p. = 163−164 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.31 (d, *J* = 7.8 Hz, 1H), 7.36–7.31 (m, 3H), 7.31–7.24 (m, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 4.13 (td, *J* = 9.2, 1.0 Hz, 2H), 3.95 (td, *J* = 9.2, 1.0 Hz, 2H), 3.87 (s, 3H), 3.54 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 162.0 (C_q), 159.7 (C_q), 143.0 (C_q), 136.9 (C_q), 131.8 (CH), 126.6 (C_q), 123.7 (C_q), 122.4 (CH), 121.7 (CH), 121.3 (CH), 113.2 (CH), 109.3 (CH), 102.1 (C_q), 66.2 (CH_2), 55.2 (CH_3), 54.6 (CH_2), 30.8 (CH_3). **IR** (ATR): 2926, 2866, 2836, 1629, 1466, 1240, 1176, 1000, 760 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 306 (40) $[M^+]$, 305 (100) $[M\text{-}H]^+$, 290 (10), 262 (20), 205 (10), 192 (10). **HR-MS** (EI) *m/z* calcd for $C_{19}H_{17}N_2O_2$ $[M\text{-}H]^+$ 305.1290, found 305.1294.



2-(2-Decyl-6-methylphenyl)-4,5-dihydrooxazole (150a): A suspension of $Co(acac)_2$ (12.9 mg, 10.0 mol %), ICy·HCl (**149g)** (13.4 mg, 10.0 mol %), oxazoline **130b** (80.6 mg, 0.50 mmol), alkyl chloride **68a** (114.9 mg, 0.65 mmol), and DMPU (1.0 mL) was stirred for 5 min at 0 °C. A solution of CyMgCl (1.0 M, 1.0 mL, 2.0 equiv) in 2-methyltetrahydrofuran was added dropwise at the same temperature. Then, the mixture was stirred at 60 °C for 16 h. At ambient temperature, aq. NH_4Cl (2.0 mL) and H_2O (15 mL) were added. The reaction mixture was extracted with MTBE (3 × 20 mL). The combined organic phase was washed with brine (20 mL) and dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification of the remaining residue by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **150a** (84.4 mg, 56%) as a colorless oil.

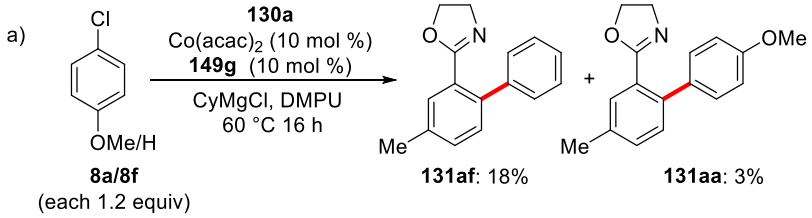
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.19 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.04–7.00 (m, 2H), 4.37 (td, *J* = 9.5, 1.0 Hz, 2H), 4.06 (td, *J* = 9.5, 1.0 Hz, 2H), 2.69–2.52 (m, 2H), 2.30 (s, 3H), 1.73–1.44 (m, 2H), 1.33–1.25 (m, 14H), 0.99–0.78 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 164.7 (C_q), 141.9 (C_q), 136.9 (C_q), 129.2 (CH), 128.6 (C_q), 127.3 (CH), 126.4 (CH), 67.0 (CH_2), 55.2 (CH_2), 33.7 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 22.6 (CH_2), 19.6 (CH_3), 14.1 (CH_3). **IR** (ATR): 2922, 2853, 1661, 1464, 1250, 1041, 938, 786 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 301 (40) $[M^+]$, 300 (5) $[M\text{-}H]^+$, 259 (10), 244 (10), 202 (10), 188 (100). **HR-MS** (EI) *m/z* calcd for $C_{20}H_{31}NO$ $[M^+]$ 301.2406, found 301.2402.



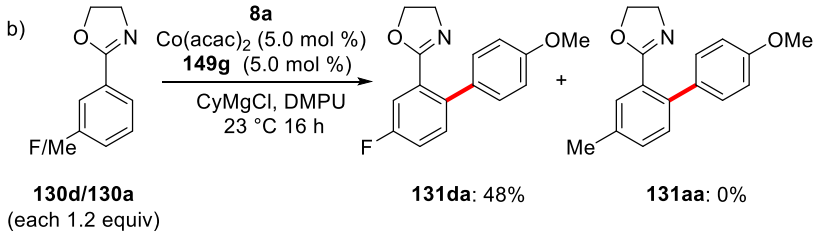
2-(2-Cyclohexyl-6-methylphenyl)-4,5-dihydrooxazole (150b): A suspension of $Co(acac)_2$ (12.9 mg, 10.0 mol %), ICy·HCl (**149g)** (13.4 mg, 10.0 mol %), oxazoline **130b** (80.6 mg, 0.50 mmol), alkyl chloride **68b** (77.1 mg, 0.65 mmol), and DMPU (1.0 mL) was stirred for 5 min at 0 °C. A solution of CyMgCl (1.0 M, 1.0 mL, 2.0 equiv) in 2-methyltetrahydrofuran was added dropwise at the same temperature. Then the mixture was stirred at 60 °C for 16 h. At ambient temperature, aq. NH_4Cl (2.0 mL) and H_2O (15 mL) were added. The reaction mixture was extracted with MTBE (3 × 20 mL). The combined organic phase was washed with brine (20 mL) and dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification of the remaining residue by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **150b** (68.1 mg, 56%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.23 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 4.38 (t, *J* = 9.5 Hz, 2H), 4.07 (t, *J* = 9.5 Hz, 2H), 2.56 (tt, *J* = 11.6, 3.2 Hz, 1H), 2.29 (s, 3H), 1.90–1.76 (m, 4H), 1.71 (dtt, *J* = 12.3, 3.1, 1.6 Hz, 1H), 1.43–1.17 (m, 5H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 164.8 (C_q), 146.7 (C_q), 136.7 (C_q), 129.4 (CH), 128.3 (C_q), 127.2 (CH), 123.2 (CH), 67.1 (CH_2), 55.2 (CH_2), 41.8 (CH), 34.3 (CH_2), 27.0 (CH_2), 26.2 (CH_2), 19.7 (CH_3). **IR** (ATR): 2923, 2850, 1659, 1465, 1249, 1041, 936, 783 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 243 (30) [M^+], 242 (15) [M-H]$^+$, 228 (10), 215 (40), 200 (30), 172 (100). **HR-MS** (EI) *m/z* calcd for $C_{16}H_{21}NO$ [M-H] $^+$ 242.1545, found 242.1536.

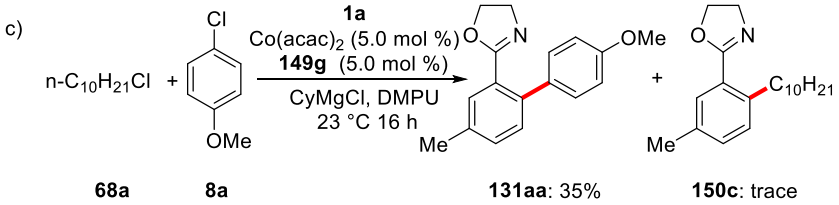
Competition Experiments



A suspension of $Co(acac)_2$ (12.9 mg, 10.0 mol %), ICy·HCl (**149g)** (13.4 mg, 10.0 mol %), aryl oxazoline **130a** (80.6 mg, 0.50 mmol), aryl chlorides **8a** (85.6 mg, 0.60 mmol) and **8f** (67.5 mg, 0.60 mmol) and DMPU (1.0 mL) was stirred for 5 min at 0 °C. A solution of CyMgCl (1.0 M, 1.0 mL, 2.0 equiv) in 2-methyltetrahydrofuran was added dropwise at the same temperature. Then the mixture was stirred at 60 °C for 16 h. At ambient temperature, aq. NH_4Cl (2.0 mL) and H_2O (15 mL) were added. The reaction mixture was extracted with MTBE (3 × 20 mL). The combined organic phase was washed with brine (20 mL) and dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification of the remaining residue by column chromatography on silica gel (*n*-hexane/EtOAc 8:1) yielded product **131af** (21.3 mg, 18%) and **131aa** (4.0 mg, 3%).



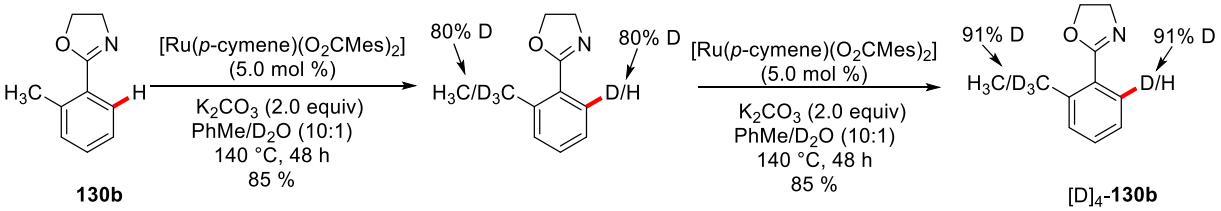
A suspension of $Co(acac)_2$ (6.4 mg, 5.0 mol %), ICy·HCl (**149g)** (6.7 mg, 5.0 mol %), aryl chloride **8a** (71.3 mg, 0.50 mmol), aryl oxazolines **130d** (99.1 mg, 0.60 mmol) and **130a** (96.7 mg, 0.60 mmol) and DMPU (1.0 mL) was stirred for 5 min at 0 °C. A solution of CyMgCl (1.0 M, 1.0 mL, 2.0 equiv) in 2-methyltetrahydrofuran was added dropwise at the same temperature. Then the mixture was stirred at 23 °C for 16 h. At ambient temperature, aq. NH_4Cl (2.0 mL) and H_2O (15 mL) were added. The reaction mixture was extracted with MTBE (3 × 20 mL). The combined organic phase was washed with brine (20 mL) and dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification of the remaining residue by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded product **131da** (65.1 mg, 48%). The product **131aa** was not detected.



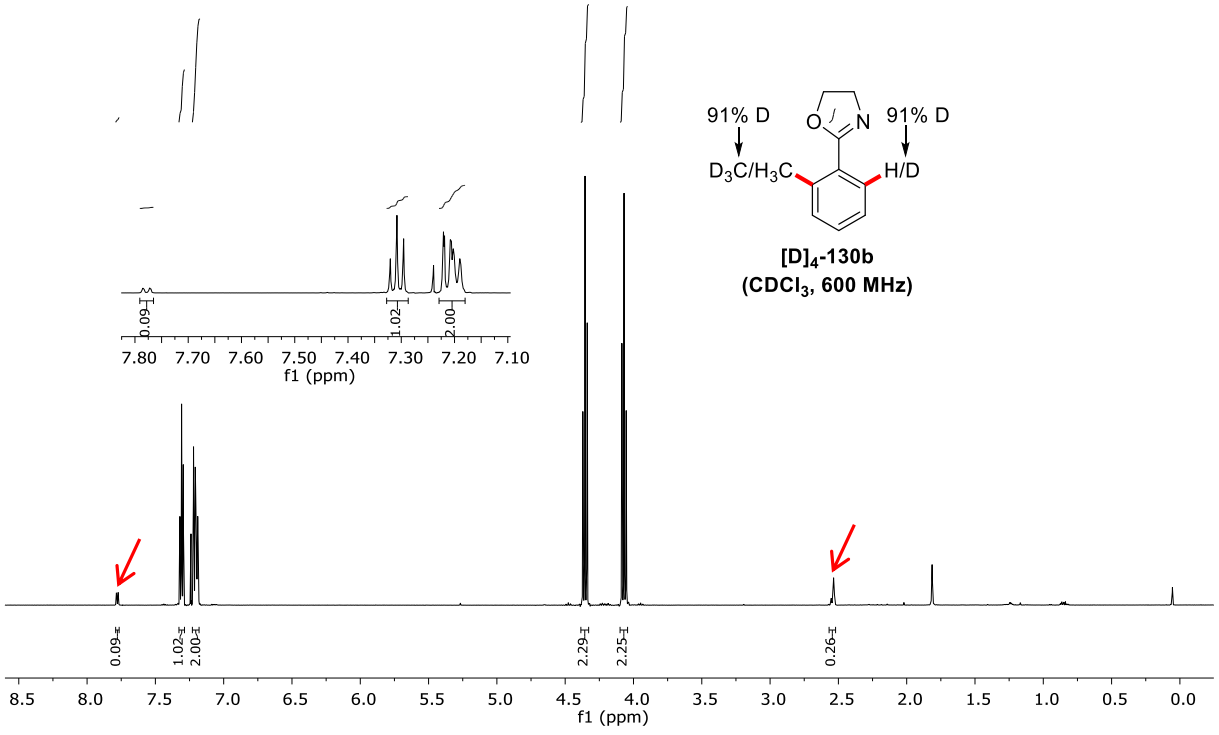
A suspension of $Co(acac)_2$ (6.4 mg, 5.0 mol %), ICy·HCl (**149g)** (6.7 mg, 5.0 mol %), aryl oxazoline **130a** (80.6 mg, 0.50 mmol), alkyl chloride **68a** (106.0 mg, 0.60 mmol) and aryl chloride **8a** (85.6 mg, 0.60 mmol) and DMPU (1.0 mL) was stirred for 5 min at 0 °C. A solution of CyMgCl (1.0 M, 1.0 mL, 2.0 equiv) in 2-methyltetrahydrofuran was added dropwise at the same temperature. Then the mixture was stirred at 23 °C for 16 h. At ambient temperature, aq. NH_4Cl (2.0 mL) and H_2O (15 mL) were added. The reaction mixture was extracted with MTBE (3 × 20 mL). The combined organic phase was washed with brine (20 mL) and dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification of the remaining residue by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded product **131aa** (46.8 mg, 35%). Only traces of alkylated arene **150c** were detected by GC-MS analysis.

Kinetic Isotope Effect Experiments

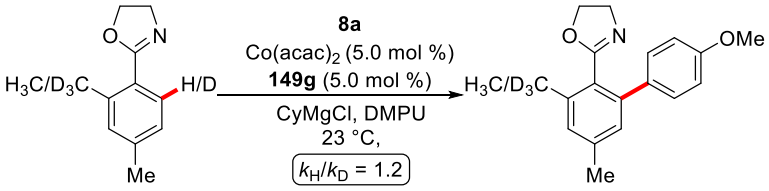
Synthesis of Deuterated Substrate $[D]_4$-130b



To a 60 mL Sealed tube was added **130b** (967 mg, 6.0 mmol), [Ru(*p*-cymene)($O_2CMes)_2$] (168 mg, 5.0 mol %), K_2CO_3 (1.66 g, 12.0 mmol), D_2O (0.80 mL), and PhMe (8.0 mL) under argon atmosphere. The mixture was stirred at 140 °C for 48 h. At ambient temperature, the reaction mixture was diluted with EtOAc (50 mL), dried with K_2CO_3 and concentrated *in vacuo*. The crude product was purified by column chromatography (*n*-hexane/EtOAc = 2:1) to give the deuterated product as a pale yellow oil (843 mg, 85%). ^{1}H-NMR analysis showed 80% deuterium incorporation in the *ortho*-position. The same procedure was repeated again. The substrate (843 mg, 5.1 mmol) was dissolved in PhMe (6.0 mL), [Ru(*p*-cymene)($O_2CMes)_2$] (143 mg, 5.0 mol %), K_2CO_3 (1.41 g, 10.2 mmol) and D_2O (0.60 mL) was added. This mixture was stirred at 140 °C for 48 h. Following the same work-up procedure as above, the deuterated product $[D]_4$-**130b** was isolated as a pale yellow oil (725 mg, 86%). ^{1}H-NMR analysis showed 91% deuterium incorporation in the *ortho*-position.



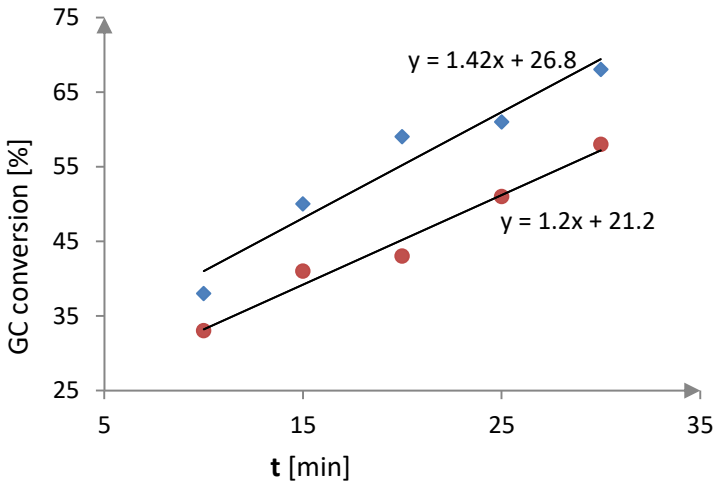
1) Parallel Experiments



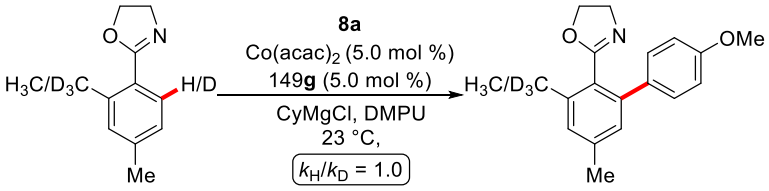
130b/[D]$_4$-**130b** **131ba**/[D]$_3$-**131ba**

Two independent reactions with **130b** or deuterated substrate [D]$_4$-**130b** under the standard conditions were performed. A suspension of Co(acac)$_2$ (6.4 mg, 5.0 mol %), ICy·HCl (**149g)** (6.7 mg, 5.0 mol %), aryl chloride **8a** (92.7 mg, 0.65 mmol), substrate **130b** (80.6 mg, 0.50 mmol) or [D]$_4$-**130b** (82.6 mg, 0.50 mmol), internal standard 1,3,5-trimethoxybenzene (16.8 mg, 0.10 mmol) and DMPU (1.0 mL) were stirred at 0 °C for 5 min. A solution of CyMgCl (1.0 M, 1.0 mL, 2.0 equiv) in 2-methyltetrahydrofuran was added dropwise at the same temperature. An aliquot (0.1 mL) was removed by syringe every 5 min. The appearance of the product **131ba** or [D]$_3$-**131ba** was monitored by GC analysis to provide the following conversions.

t [min]	10	15	20	25	30
131ba [%]	38	50	59	61	68
[D]$_3$-131ba [%]	33	41	43	51	58

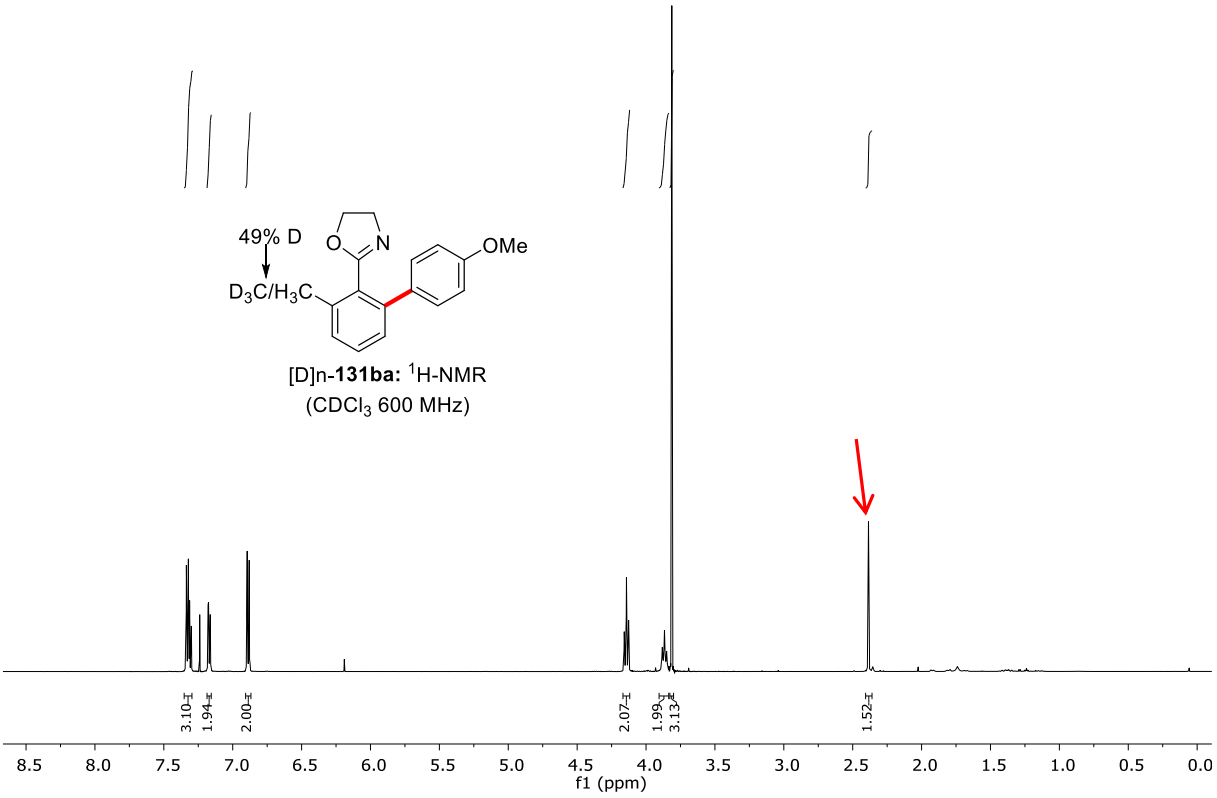


2) Competition Experiment

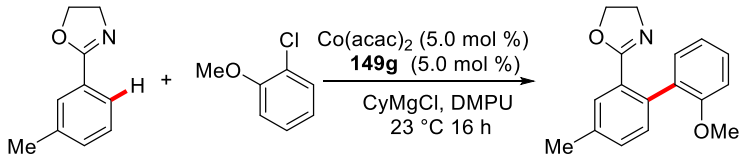


130b/[D]$_4$-**130b** [D]$_n$-**131ba**

A suspension of Co(acac)$_2$ (6.4 mg, 5.0 mol %), ICy·HCl (**149g)** (6.7 mg, 5.0 mol %), aryl chloride **8a** (71.3 mg, 0.50 mmol), substrate **130b** (80.6 mg, 0.50 mmol) and [D]$_4$-**130b** (82.6 mg, 0.50 mmol) in DMPU (1.0 mL) were stirred at 0 °C for 5 min. A solution of CyMgCl (1.0 M, 1.0 mL, 2.0 equiv) in 2-methyltetrahydrofuran was added dropwise at the same temperature. Then the mixture was stirred at 23 °C for 1 h. Then aq. NH_4Cl (2.0 mL) and H_2O (15 mL) were added. The reaction mixture was extracted with MTBE (3 × 20 mL). The combined organic phase was washed with brine (20 mL) and dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification of the remaining residue by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded product [D]$_n$-**131ba** (24 mg, 18%) as a colorless oil. The KIE value of the competition experiment was estimated to be 1.0 by ^{1}H NMR analysis.



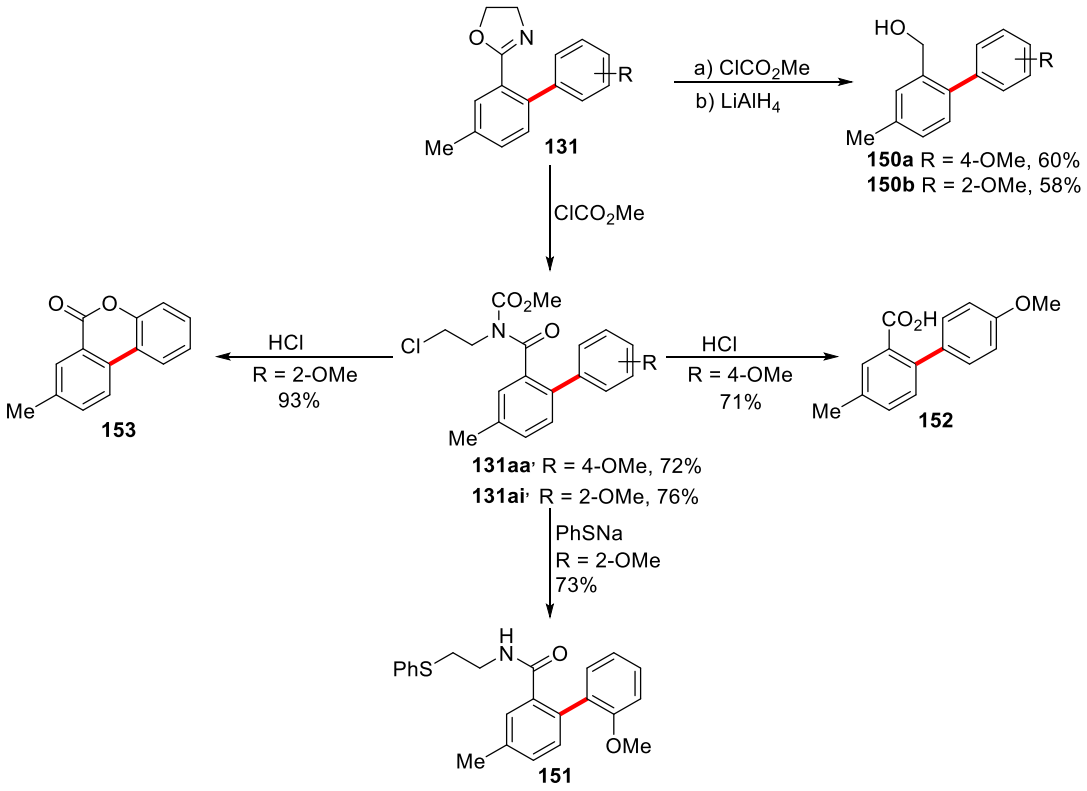
Procedure for Gram-Scale Reaction



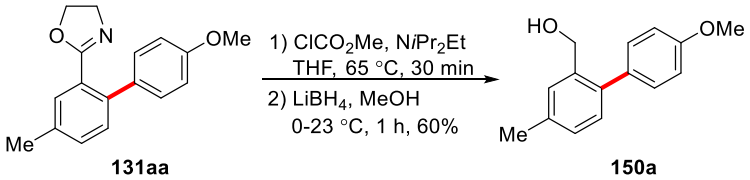
130a **8i** **131ai**:1.56 g, 73%

A suspension of $Co(acac)_2$ (102.9 mg, 5.0 mol %), ICy·HCl (**149g)** (107.5 mg, 10.0 mol %), aryl oxazoline **130a** (1.29 g, 8.0 mmol), alkyl chlorides **8i** (1.48 g, 10.4 mmol), and DMPU (8.0 mL) was stirred for 5 min at 0 °C. A solution of CyMgCl (1.0 M, 16 mL, 2.0 equiv) in 2-methyltetrahydrofuran was added dropwise at the same temperature. Then, the mixture was stirred at 23 °C for 16 h. At ambient temperature, aq. NH_4Cl (20.0 mL) and H_2O (80 mL) were added. The reaction mixture was extracted with MTBE (3 × 100 mL). The combined organic phase was washed with brine (100 mL) and dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification of the remaining residue by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded product **131ai** (1.56 g, 73%) as a yellow oil.

Diversification of Oxazolines 131



(4'-Methoxy-4-methyl-[1,1'-biphenyl]-2-yl)methanol (150a)

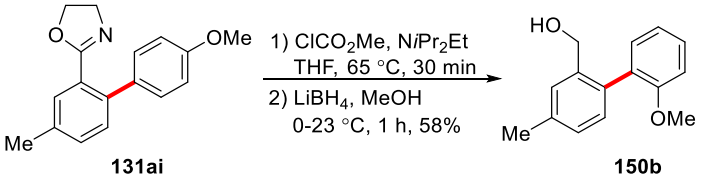


131aa **150a**

A 25 mL round-bottomed flask was charged with the oxazoline **131aa** (534.7 mg, 2.0 mmol), THF (3.0 mL), Hünig's base (51.7 mg, 0.4 mmol), and methyl chloroformate (378.0 mg, 4.0 mmol). The reaction mixture was then heated to 65 °C and stirred for 30 min before being cooled to 0 °C. Then, $LiAlH_4$ (228 mg, 6.0 mmol) was added, followed by MeOH (192.2 mg, 6.0 mmol), the reaction was then warmed to ambient temperature and stirred for 1 h. The reaction mixture was cooled to 0 °C and carefully quenched with HCl (1.0 N, 2.5 mL) and H_2O (2.5 mL). After 15 min, the reaction mixture was diluted with H_2O (25 mL). The reaction mixture was extracted with MTBE (3 × 30 mL). The combined organic phase was washed with brine (50 mL) and dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification of the remaining residue by column chromatography (*n*-hexane/EtOAc 5:1) yielded product **150a** (273.9 mg, 60%) as colorless solid.

M. p. = 97–98 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.34 (dd, J = 2.4, 0.7 Hz, 1H), 7.28 (d, J = 8.8 Hz 2H), 7.18–7.13 (m, 2H), 6.94 (d, J = 8.8 Hz 2H), 4.58 (s, 2H), 3.83 (s, 3H), 2.39 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 158.7 (C_q), 138.1 (C_q), 137.8 (C_q), 137.1 (C_q), 133.0 (C_q), 130.2 (CH), 130.1 (CH), 129.1 (CH), 128.3 (CH), 113.6 (CH), 63.2 (CH_2), 55.2 (CH_3), 21.1 (CH_3). **IR** (ATR): 3329, 2912, 1609, 1484, 1244, 1033, 840, 532 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 229 (10) [M+H$^+$], 228 (100) [M$^+$], 210 (40), 195 (60), 185 (10), 152 (30). **HR-MS** (EI) *m/z* calcd for $C_{15}H_{16}O_2$ [M$^+$] 228.1150, found 228.1146.

(2'-Methoxy-4-methyl-[1,1'-biphenyl]-2-yl)methanol (150b)[103b]



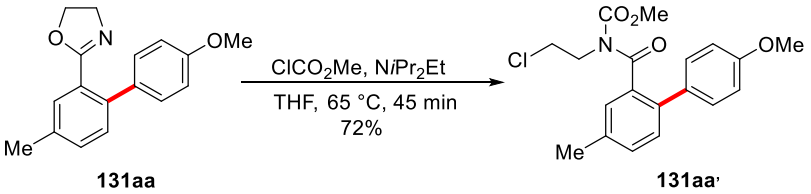
131ai **150b**

A 25 mL round-bottomed flask was charged with the oxazoline **131ai** (534.7 mg, 2.0 mmol), THF (3.0 mL), Hünig's base (51.7 mg, 0.4 mmol), and methyl chloroformate (378.0 mg, 4.0 mmol). The reaction mixture was then heated to 65 °C and stirred for 30 min before being cooled to 0 °C. Then, $LiAlH_4$ (228 mg, 6.0 mmol) was added, followed by MeOH (192.2 mg, 6.0 mmol), the reaction was then warmed to ambient temperature and stirred for 1 h. The reaction mixture was cooled to 0 °C and carefully quenched with HCl (1.0 N, 2.5 mL) and H_2O (2.5 mL). After 15 min of stirring, the reaction mixture was diluted with H_2O (25 mL).The reaction mixture was extracted with MTBE (3 × 30 mL). The combined organic phase was washed with brine (50 mL) and dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification of the remaining residue by

column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded product **150b** (264.8 mg, 58%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.42–7.32 (m, 2H), 7.23–7.09 (m, 3H), 7.08–6.95 (m, 2H), 4.41 (d, J = 11.7 Hz, 2H), 3.75 (s, 3H), 2.43 (s, 3H), 2.38 (br, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 156.3 (C_q), 139.0 (C_q), 137.5 (C_q), 134.4 (C_q), 131.3 (CH), 130.1 (CH), 129.7 (C_q), 129.0 (CH), 128.8 (CH), 128.3 (CH), 120.9 (CH), 110.9 (CH), 63.5 (CH_2), 55.6 (CH_3), 21.1 (CH_3). **IR** (ATR): 3392, 2938, 1734, 1596, 1481, 1230, 1051, 749 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 229 (10) [M+H$^+$], 228 (100) [M$^+$], 210 (20), 195 (60), 185 (10), 152 (30). **HR-MS** (EI) *m/z* calcd for $C_{15}H_{16}O_2$ [M$^+$] 228.1150, found 228.1147.

Methyl (2-chloroethyl)(4'-methoxy-4-methyl-[1,1'-biphenyl]-2-carbonyl)carbamate (131aa')

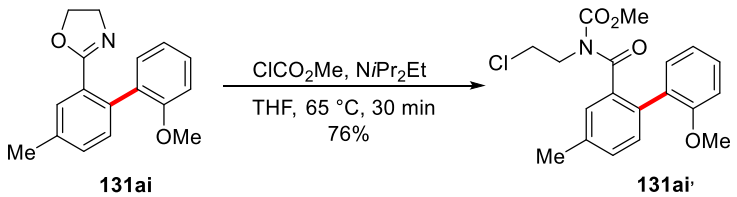


131aa **131aa'**

A 25 mL round-bottomed flask was charged with the oxazoline **131aa** (534.7 mg, 2.0 mmol), THF (3.0 mL), Hünig's base (51.7 mg, 0.4 mmol), and methyl chloroformate (378.0 mg, 4.0 mmol). The reaction mixture was then heated to 65 °C and stirred for 45 min, before being cooled to ambient temperature. Then the solvent was removed and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) to afford **131aa'** (521.0 mg, 72%) as a white solid.

M. p. = 89–90 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.28–7.15 (m, 5H), 6.92–6.85 (m, 2H), 3.87 (t, J = 7.0 Hz, 2H), 3.81 (s, 3H), 3.48 (s, 3H), 3.49 (t, J = 7.0 Hz, 2H), 2.39 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ =172.7 (C_q), 159.2 (C_q), 153.9 (C_q), 136.7 (C_q), 136.1 (C_q), 135.9 (C_q), 132.3 (C_q), 130.8 (CH), 129.6 (CH), 129.3 (CH), 127.5 (CH), 113.7 (CH), 55.3 (CH_3), 53.6 (CH_3), 45.9 (CH_2), 40.7 (CH_2), 21.0 (CH_3). **IR** (ATR): 2967, 2839, 1741, 1687, 1443, 1337, 1196, 846 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 362 (50) [M+H$^+$], 326 (30), 286 (10), 225 (100), 197 (10). **HR-MS** (EI) *m/z* calcd for $C_{19}H_{20}ClNO_4$ [M+H$^+$] 362.1154, found 362.1150.

Methyl (2-chloroethyl)(2'-methoxy-4-methyl-[1,1'-biphenyl]-2-carbonyl)carbamate (131ai')

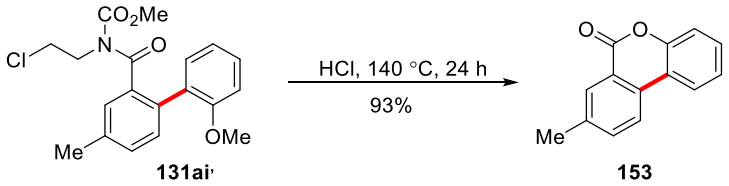


131ai **131ai'**

A 25 mL round-bottomed flask was charged with the oxazoline **131ai** (534.7 mg, 2.0 mmol), THF (3.0 mL), Hünig's base (51.7 mg, 0.4 mmol), and methyl chloroformate (378.0 mg, 4.0 mmol). The reaction mixture was then heated to 65 °C and stirred for 45 min, before being cooled to ambient temperature. Then, the

solvent was removed and the residue was purified by column afford **131ai'** (549.9 mg, 76%) as a white solid. **M. p.** = 117−118 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.36–7.34 (m, 1H), 7.33–7.26 (m, 2H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.12 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.96 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 6.88 (dd, *J* = 8.3, 1.1 Hz, 1H), 3.72 (t, *J* = 7.2 Hz, 2H), 3.69 (s, 3H), 3.44 (s, 3H), 3.41 (t, *J* = 7.2 Hz, 2H), 2.40 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 172.5 (C_q), 156.3 (C_q), 153.9 (C_q), 137.2 (C_q), 136.5 (C_q), 132.8 (C_q), 131.0 (CH), 131.0 (CH), 130.4 (CH), 129.3 (CH), 128.5 (C_q), 128.3 (CH), 120.6 (CH), 110.4 (CH), 55.2 (CH_3), 53.4 (CH_3), 46.1 (CH_2), 40.5 (CH_2), 21.1 (CH_3). **IR** (ATR): 2954, 2839, 1722, 1661, 1442, 1342, 1261, 755 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 362 (40) [M+H$^+$], 326 (10), 301 (5), 225 (100), 173 (10), 149 (5). **HR-MS** (ESI) *m/z* calcd for $C_{19}H_{20}ClNO_4Na$ [M+Na$^+$] 384.0973, found 384.0971.

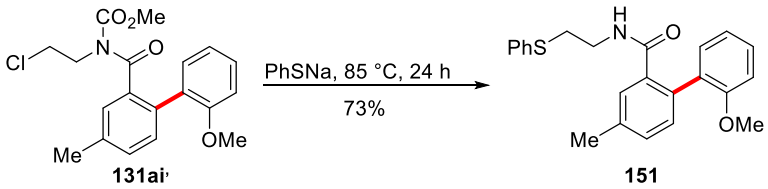
8-Methyl-6*H*-benzo[*c*]chromen-6-one (12i)



A 20 mL seal tube was charged with amide **131ai'** (361.8 mg, 1.0 mmol), aqueous HCl (5.0 mL, 37%) and then stirred at 140 °C for 24 h. The mixture was allowed to cool to ambient temperature. H_2O (20 mL) was carefully added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification of the remaining residue by column chromatography on silica gel (*n*-hexane/EtOAc 10:1) yielded product **153** (195.5 mg, 93%) as a white solid. **M. p.** = 130−131 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.17 (s, 1H), 8.04–7.95 (m, 2H), 7.61 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.43 (ddd, *J* = 8.2, 7.0, 1.6 Hz, 1H), 7.36–7.26 (m, 2H), 2.47 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 161.3 (C_q), 151.0 (C_q), 139.2 (C_q), 136.0 (CH), 132.2 (C_q), 130.3 (CH), 129.9 (CH), 124.4 (CH), 122.5 (CH), 121.6 (CH), 121.1 (C_q), 118.2 (C_q), 117.7 (CH), 21.3 (CH_3). **IR** (ATR): 2919, 1719, 1611, 1477, 1305, 1175, 1112, 744 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 211 (10) [M+H$^+$], 210 (100) [M$^+$], 181 (30), 165 (15), 152 (30). **HR-MS** (EI) *m/z* calcd for $C_{14}H_{10}O_2$ [M$^+$] 210.0681, found 210.0673.

The analytical data are in accordance with those previously reported in the literature.[105d]

2'-Methoxy-4-methyl-N-[2-(phenylthio)ethyl]-[1,1'-biphenyl]-2-carboxamide (151)

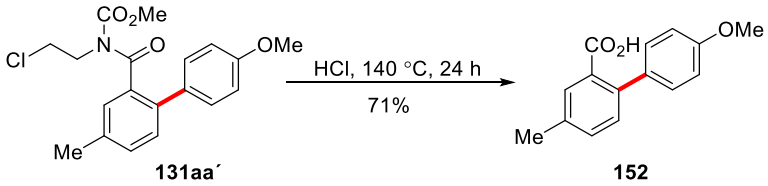


A 20 mL seal tube was charged with the amide **131ai'** (180.9 mg, 0.5 mmol), PhSNa (330.4 mg, 2.5 mmol) and MeOH (2.0 mL). The mixture was stirred at 85 °C for 24 h. At ambient temperature, the solvent was

removed and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) to yield product **151** (1.56 g, 73%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55 (dd, *J* = 1.3, 0.6 Hz, 1H), 7.40–7.09 (m, 9H), 7.01 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 6.91 (dd, *J* = 8.3, 1.0 Hz, 1H), 5.93 (t, *J* = 5.4 Hz, 1H), 3.74 (s, 3H), 3.31 (t, *J* = 6.4 Hz, 2H), 2.67 (t, *J* = 6.5 Hz, 2H), 2.40 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 169.0 (C_q), 156.3 (C_q), 137.4 (C_q), 135.7 (C_q), 134.7 (C_q), 132.8 (C_q), 130.8 (CH), 130.7 (CH), 130.7 (CH), 129.6 (CH), 129.3 (CH), 129.2 (C_q), 128.9 (CH), 128.9 (CH), 126.3 (CH), 120.9 (CH), 110.7 (CH), 55.4 (CH_3), 38.4 (CH_2), 33.2 (CH_2), 21.1 (CH_3). **IR** (ATR): 3417, 2935, 1719, 1644, 1503, 1249, 1024, 736 cm^{-1}. **HR-MS** (ESI) *m/z* calcd for $C_{23}H_{23}NO_2SNa$ [M+Na$^+$] 400.1342, found 400.1332.

4'-Methoxy-4-methyl-[1,1'-biphenyl]-2-carboxylic acid (152)



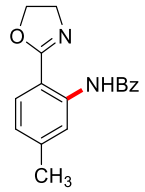
131aa´ **152**

A 20 mL seal tube was charged with amide **131aa'** (361.8 mg, 1.0 mmol), HCl (5.0 mL, 37%) and then stirred at 140 °C for 24 h. The mixture was allowed to cool to ambient temperature. H_2O (20 mL) was carefully added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification of the remaining residue by column chromatography (*n*-hexane/EtOAc 10:1) and then by HPLC yielded product **152** (172.0 mg, 71%) as a pale yellow solid.

M. p. = 108−109 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 10.28 (br, H),7.73 (dd, *J* = 1.3, 0.6 Hz, 1H), 7.37–7.30 (m, 1H), 7.27–7.19 (m, 3H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 2.40 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 173.8 (C_q), 158.9 (C_q), 140.1 (C_q), 136.6 (C_q), 133.3 (C_q), 132.8 (CH), 131.1 (CH), 131.1 (CH), 129.6 (CH), 129.0 (C_q), 113.5 (CH), 55.2 (CH_3), 20.8 (CH_3). **IR** (ATR): 2947, 1678, 1608, 1285, 1038, 823 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 243 (20) [M+H$^+$], 242 (100) [M$^+$], 225 (20), 181 (20), 153 (20). **HR-MS** (EI) *m/z* calcd for $C_{15}H_{14}O_3$ [M$^+$] 242.0943, found 242.0941.

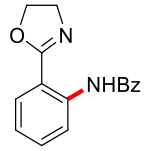
The analytical data are in accordance with those previously reported in the literature.[149]

5.3.5 Oxazoline-Assisted C–H Amidation by Cobalt(III) Catalysis



***N*-[2-(4,5-Dihydrooxazol-2-yl)-5-methylphenyl]benzamide (133ia)**: The general procedure **E** was followed using oxazoline **130i** (81 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **133ia** (95 mg, 68%) as a white solid.

M. p. = 149−150 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 13.00 (s, 1H), 8.82 (s, 1H), 8.10 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 8.0 Hz, 1H), 7.58–7.45 (m, 3H), 6.92 (dd, J = 8.0, 1.4 Hz, 1H), 4.41–4.33 (m, 2H), 4.19–4.14 (m, 2H), 2.43 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.0 (C_q), 164.9 (C_q), 143.4 (C_q), 140.0 (C_q), 135.3 (C_q), 131.5 (CH), 129.1 (CH), 128.5 (CH), 127.7 (CH), 123.3 (CH), 120.3 (CH), 111.0 (C_q), 66.1 (CH_2), 54.6 (CH_2), 22.1 (CH_3). **IR** (ATR): 3055, 2982, 2915, 1677, 1363, 1155, 1103, 1055, 817, 754 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 281 (20) [M+H$^+$], 280 (55), 263 (25), 203 (100), 160 (50). **HR-MS** (EI) *m/z* calcd for $C_{17}H_{16}N_2O_2$ [M$^+$] 280.1212, found 280.1212.

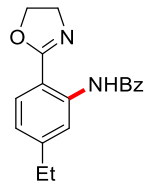


***N*-[2-(4,5-Dihydrooxazol-2-yl)phenyl]benzamide (133ja)**: The general procedure **E** was followed using oxazoline **130j** (74 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 11:2) yielded **133ja** (95 mg, 71%) as a white solid.

M. p. = 143–145 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 13.03 (s, 1H), 8.97 (dd, J = 8.5, 1.2 Hz, 1H), 8.10 (d, J = 8.1 Hz, 2H), 7.91 (dd, J = 7.9, 1.7 Hz, 1H), 7.59–7.45 (m, 4H), 7.12 (ddd, J = 7.9, 7.3, 1.2 Hz, 1H), 4.42 (td, J = 9.4, 1.1 Hz, 2H), 4.21 (td, J = 9.4, 1.1 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.2 (C_q), 165.1 (C_q), 140.4 (C_q), 135.5 (C_q), 132.8 (CH), 131.8 (CH), 129.4 (CH), 128.7 (CH), 127.9 (CH), 122.5 (CH), 120.1 (CH), 113.7 (C_q), 66.4 (CH_2), 54.9 (CH_2). **IR** (ATR): 3026, 1614, 1446, 1303, 1058, 943, 748, 703, 674 cm^{-1}. **MS**

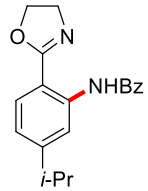
(EI) *m/z* (relative intensity) 266 (56) [M^+], 189 (96), 146 (42), 105 (100), 77 (75), 51 (12). **HR-MS** (ESI) *m/z* calcd for $C_{16}H_{13}N_2O_2$ [M-H]$^-$: 265.0983, found: 265.0991.

The analytical data are in accordance with those previously reported in the literature.[150]



***N*-[2-(4,5-Dihydrooxazol-2-yl)-5-ethylphenyl]benzamide (133ka)**: The general procedure **E** was followed using oxazoline **130k** (88 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 7:1) yielded **133ka** (95 mg, 65%) as a white solid.

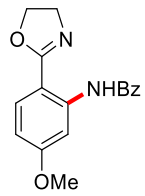
M. p. = 122–124 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 13.02 (s, 1H), 8.87 (dq, *J* = 1.8, 0.6 Hz, 1H), 8.17–8.05 (m, 2H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.61–7.43 (m, 3H), 6.96 (ddt, *J* = 8.1, 1.7, 0.6 Hz, 1H), 4.40 (td, *J* = 9.1, 1.0 Hz, 2H), 4.19 (td, *J* = 9.1, 1.0 Hz, 2H), 2.74 (q, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.1 (C_q), 165.0 (C_q), 149.8 (C_q), 140.3 (C_q), 135.5 (C_q), 131.6 (CH), 129.3 (CH), 128.6 (CH), 127.8 (CH), 122.2 (CH), 119.4 (CH), 111.3 (C_q), 66.3 (CH_2), 54.8 (CH_2), 29.6 (CH_2), 15.5 (CH_3). **IR** (ATR): 3065, 2962, 1620, 1580, 1296, 1242, 1052, 698, 678 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 294 (49) [M^+], 277 (14), 217 (100), 174 (36), 105 (47), 77 (49). **HR-MS** (EI) *m/z* calcd for $C_{18}H_{18}N_2O_2$ [M^+]: 294.1368, found: 294.1376.



***N*-[2-(4,5-Dihydrooxazol-2-yl)-5-isopropylphenyl]benzamide (133la)**: The general procedure **E** was followed using oxazoline **130l** (95 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **133la** (103 mg, 67%) as a white solid.

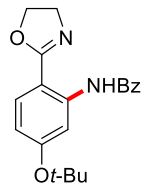
M. p. = 137−139 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 13.00 (s, 1H), 8.89 (d, *J* = 1.8 Hz, 1H), 8.13–8.05 (m, 2H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.56–7.43 (m, 3H), 6.97 (ddd, *J* = 8.2, 1.8, 0.5 Hz, 1H), 4.42–4.31 (m, 2H), 4.18–4.13 (m, 2H), 2.98 (hept, *J* = 6.9 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.1 (C_q), 164.9 (C_q), 154.3 (C_q), 140.2 (C_q), 135.4 (C_q), 131.5 (CH), 129.2 (CH), 128.5 (CH), 127.7 (CH),

120.6 (CH), 118.0 (CH), 111.3 (C_q), 66.2 (CH_2), 54.6 (CH_2), 34.6 (CH), 23.7 (CH_3). **IR** (ATR): 3027, 2959, 2869, 1663, 1624, 1426, 1289, 1239, 1050, 694 cm^{-1}. **MS** (EI) m/z (relative intensity) 308 (60) [M^+], 291 (25), 231 (100), 188 (40), 105 (60). **HR-MS** (EI) m/z calcd for $C_{19}H_{20}N_2O_2$ [M^+] 308.1512, found 308.1524.



***N*-[2-(4,5-Dihydrooxazol-2-yl)-5-methoxyphenyl]benzamide (133ma)**: The general procedure **E** was followed using oxazoline **130m** (89 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **133ma** (111 mg, 75%) as a white solid.

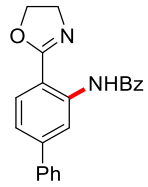
M. p. = 178−179 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 13.15 (s, 1H), 8.66 (d, *J* = 2.6 Hz, 1H), 8.11–8.06 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.54–7.51 (m, 1H), 7.50–7.46 (m, 2H), 6.63 (dd, *J* = 8.8, 2.6 Hz, 1H), 4.36 (td, *J* = 9.2, 0.9 Hz, 2H), 4.19–4.11 (td, *J* = 9.2, 0.9 Hz, 2H), 3.89 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 166.3 (C_q), 164.8 (C_q), 162.9 (C_q), 142.0 (C_q), 135.2 (C_q), 131.7 (CH), 130.5 (CH), 128.6 (CH), 127.7 (CH), 109.7 (CH), 106.4 (C_q), 104.0 (CH), 66.1 (CH_2), 55.5 (CH_3), 54.5 (CH_2). **IR** (ATR): 3062, 2882, 1636, 1613, 1411, 1283, 1242, 1143, 938, 753 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 296 (5) [M^+], 267 (25), 240 (10), 219 (10), 105 (100), 77 (60). **HR-MS**: (EI) *m/z* calcd for $C_{17}H_{16}N_2O_3$ [M^+] 296.1161, found 296.1167.



***N*-[5-(*tert*-Butoxy)-2-(4,5-dihydrooxazol-2-yl)phenyl]benzamide (133na)**: The general procedure **E** was followed using oxazoline **130n** (110 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 7.5:1) yielded **133na** (84 mg, 50%) as a white solid.

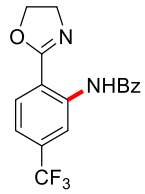
M. p. = 120–122 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 13.05 (s, 1H), 8.76 (d, *J* = 2.4 Hz, 1H), 8.13–8.07 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 8.7 Hz, 1H), 7.57–7.45 (m, 3H), 6.70 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.36 (td, *J* = 9.3, 0.9 Hz, 2H), 4.15 (td, *J* = 9.3, 0.9 Hz, 2H), 1.49 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.3 (C_q), 164.9 (C_q), 159.8 (C_q), 141.2 (C_q), 135.4 (C_q), 131.7 (CH), 130.0 (CH), 127.8 (CH), 127.8 (CH), 116.8 (CH), 113.1 (CH), 108.0 (C_q), 79.6 (C_q), 66.2 (CH_2), 54.6 (CH_2), 29.1 (CH_3). **IR** (ATR): 2978, 2935, 2877, 1630, 1578,

1362, 1257, 1239, 707 cm^{-1}. MS (EI) *m/z* (relative intensity) 338 (7) [M^+], 282 (67), 205 (100), 162 (19), 105 (83), 77 (53), 57 (24). **HR-MS** (EI) *m/z* calcd for $C_{20}H_{22}N_2O_3$ [M^+]: 338.1630, found: 338.1627.



***N*-[4-(4, 5-Dihydrooxazol-2-yl)-[1,1'-biphenyl]-3-yl]benzamide (133oa)**: The general procedure **E** was followed using oxazoline **130o** (112 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 6:1) yielded **133oa** (127 mg, 74%) as a white solid.

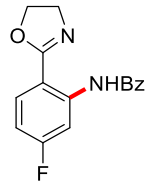
M. p. = 170–171 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 13.08 (s, 1H), 9.34 (d, *J* = 1.8 Hz, 1H), 8.12 (d, *J* = 8.1 Hz, 2H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.80–7.69 (m, 2H), 7.62–7.32 (m, 7H), 4.41 (td, *J* = 9.2, 0.9 Hz, 2H), 4.21 (td, *J* = 9.2, 0.9 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.3 (C_q), 165.0 (C_q), 145.3 (C_q), 140.7 (C_q), 140.2 (C_q), 135.4 (C_q), 131.8 (CH), 129.8 (CH), 128.9 (CH), 128.7 (CH), 128.2 (CH), 127.9 (CH), 127.5 (CH), 121.1 (CH), 118.5 (CH), 112.5 (C_q), 66.4 (CH_2), 54.9 (CH_2). **IR** (ATR): 3056, 1618, 1569, 1409, 1249, 1064, 697, 678 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 342 (64) [M^+], 265 (100), 222 (35), 166 (15), 105 (55), 77 (57). **HR-MS** (EI) *m/z* calcd for $C_{22}H_{18}N_2O_2$ [M^+]: 342.1368, found: 342.1364.



***N*-[2-(4,5-Dihydrooxazol-2-yl)-5-(trifluoromethyl)phenyl]benzamide (133pa)**: The general procedure **E** was followed using oxazoline **130p** (108 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 85:15) yielded **133pa** (106 mg, 63%) as a white solid.

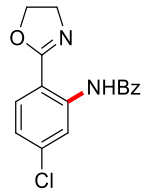
M. p. = 191–193 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 13.10 (s, 1H), 9.34 (d, *J* = 1.8 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 2H), 8.02–7.93 (m, 1H), 7.63–7.44 (m, 3H), 7.33 (ddd, *J* = 8.3, 1.8, 0.7 Hz, 1H), 4.46 (td, *J* = 9.3, 1.3 Hz, 2H), 4.24 (td, *J* = 9.3, 1.3 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.2 (C_q), 164.2 (C_q), 140.6 (C_q), 134.7 (C_q), 134.1 (q, $^2J_{C\text{-}F}$ = 32.7 Hz, C_q), 132.0 (CH), 129.8 (CH), 128.7 (CH), 127.7 (CH), 123.6 (q, $^1J_{C\text{-}F}$ = 273.1 Hz, C_q), 118.7 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, CH), 116.9 (q, $^3J_{C\text{-}F}$ = 4.2 Hz, CH), 116.0 (C_q), 66.5 (CH_2), 54.8 (CH_2). **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -63.2 (s). **IR** (ATR): 3016, 1622, 1588, 1426, 1333, 1118, 1081, 1055, 922, 899,

701 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 334 (28) [M^+], 257 (36), 214 (14), 158 (7), 105 (100), 77 (44), 51 (6). **HR-MS** (ESI) *m/z* calcd for $C_{17}H_{14}N_2O_2F_3$ [$M+H^+$]: 335.1002, found: 335.1005.



***N*-[2-(4,5-Dihydrooxazol-2-yl)-5-fluorophenyl]benzamide (133qa)**: The general procedure **E** was followed using oxazoline **130q** (83 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 85:15) yielded **133qa** (101 mg, 71%) as a white solid.

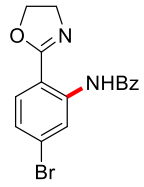
M. p. = 163–165 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 13.16 (s, 1H), 8.79 (dd, *J* = 12.2, 2.6 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 2H), 7.88 (dd, *J* = 8.9, 6.5 Hz, 1H), 7.62–7.43 (m, 3H), 6.80 (ddd, *J* = 8.9, 7.6, 2.6 Hz, 1H), 4.41 (td, *J* = 9.2, 1.3 Hz, 2H), 4.19 (td, *J* = 9.2, 1.3 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.2 (C_q), 165.0 (d, $^1J_{C\text{-}F}$ = 249.0 Hz, C_q), 164.4 (C_q), 142.1 (d, $^3J_{C\text{-}F}$ = 12.8 Hz, C_q), 134.9 (C_q), 131.9 (CH), 131.1 (d, $^3J_{C\text{-}F}$ = 10.4 Hz, CH), 128.6 (CH), 127.8 (CH), 109.8 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, C_q), 109.5 (d, $^2J_{C\text{-}F}$ = 22.5 Hz, CH), 107.3 (d, $^2J_{C\text{-}F}$ = 28.8 Hz, CH), 66.3 (CH_2), 54.6 (CH_2). **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -104.2 (m). **IR** (ATR): 3111, 2975, 1614, 1599, 1544, 1430, 1255, 705 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 284 (33) [M^+], 207 (84), 164 (30), 105 (100), 77 (45), 44 (10). **HR-MS** (ESI) *m/z* calcd for $C_{16}H_{14}N_2O_2F$ [$M+H^+$]: 285.1034, found: 285.1038.



***N*-[5-Chloro-2-(4, 5-dihydrooxazol-2-yl)phenyl]benzamide (133ra)**: The general procedure **E** was followed using oxazoline **130r** (74 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 11:2) yielded **133ra** (95 mg, 65%) as a white solid.

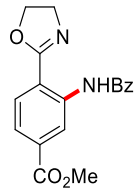
M. p. = 186−187 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 13.04 (s, 1H), 9.05 (d, *J* = 2.1 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.56–7.51 (m, 1H), 7.51–7.45 (m, 2H), 7.06 (dd, *J* = 8.5, 2.1 Hz, 1H), 4.40 (td, *J* = 9.2, 1.1 Hz, 2H), 4.18 (td, *J* = 9.2, 1.1 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.1 (C_q), 164.4 (C_q), 141.0 (C_q), 138.7 (C_q), 134.9 (C_q), 131.9 (CH), 130.2 (CH), 128.6 (CH), 127.7 (CH), 122.6 (CH), 119.9 (CH), 111.8 (C_q), 66.3 (CH_2), 54.7 (CH_2). **IR** (ATR): 3063, 2880, 1674, 1613, 1579, 1358, 1281, 1237, 1057,

691 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 300 (20) [M^+] (^{35}Cl), 223 (55), 180 (25), 124 (10), 105 (100), 77 (60). **HR-MS** (EI) *m/z* calcd for $C_{16}H_{13}{}^{35}ClN_2O_2$ [M^+] 300.0666, found 300.0659.



***N*-[5-Bromo-2-(4,5-dihydrooxazol-2-yl)phenyl]benzamide (133sa)**: The general procedure **E** was followed using oxazoline **130s** (113 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 11:2) yielded **133sa** (88 mg, 51%) as a white solid.

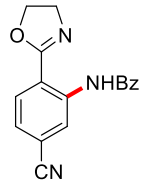
M. p. = 139−140 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 13.02 (s, 1H), 9.21 (d, *J* = 2.0 Hz, 1H), 8.08–8.01 (d, *J* = 8.2 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.56–7.51 (m, 1H), 7.51–7.45 (m, 2H), 7.22 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.40 (td, *J* = 9.3, 1.2 Hz, 2H), 4.17 (td, *J* = 9.3, 1.2 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.1 (C_q), 164.5 (C_q), 141.0 (C_q), 134.8 (C_q), 131.9 (CH), 130.3 (CH), 128.6 (CH), 127.7 (CH), 127.3 (C_q), 125.5 (CH), 122.8 (CH), 112.2 (C_q), 66.3 (CH_2), 54.7 (CH_2). **IR** (ATR): 3062, 2935, 1672, 1626, 1443, 1039, 856, 753, 523 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 346 (15) [M^+] (^{81}Br), 344 (16) [M^+] (^{79}Br), 269 (31) (^{81}Br), 267 (32) (^{79}Br), 207 (17), 105 (100), 77 (54). **HR-MS** (EI) *m/z* calcd for $C_{16}H_{13}{}^{79}BrN_2O_2$ [M^+] 344.0160, found 344.0160.



Methyl 3-benzamido-4-(4, 5-dihydrooxazol-2-yl)benzoate (133ta): The general procedure **E** was followed using oxazoline **130t** (103 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **133ta** (115 mg, 71%) as a white solid.

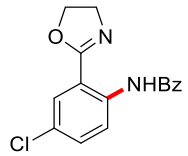
M. p. = 148−149 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 12.98 (s, 1H), 9.57 (d, *J* = 1.6 Hz, 1H), 8.07 (d, *J* = 7.9 Hz, 2H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.75 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.56–7.44 (m, 3H), 4.42 (td, *J* = 9.4, 1.3 Hz, 2H), 4.20 (td, *J* = 9.4, 1.3 Hz, 2H), 3.93 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 166.5 (C_q), 166.0 (C_q), 164.4 (C_q), 140.2 (C_q), 134.9 (C_q), 133.6 (C_q), 131.8 (CH), 129.3 (CH), 128.6 (CH), 127.7 (CH), 123.2 (CH), 120.7 (CH), 116.8 (C_q), 66.4 (CH_2), 54.8 (CH_2), 52.4 (CH_3). **IR** (ATR): 3115, 3053, 2952, 1721, 1617, 1579, 1288,

1258, 1101, 745 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 324 (19) [M^+], 307 (5), 293 (5), 247 (20), 220 (40), 105 (100). **HR-MS** (EI) *m/z* calcd for $C_{18}H_{16}N_2O_4$ [M^+] 324.1110, found 324.1107.



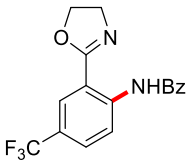
***N*-[5-Cyano-2-(4,5-dihydrooxazol-2-yl)phenyl]benzamide (133ua)**: The general procedure **E** was followed using oxazoline **130u** (91 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) yielded **133ua** (99 mg, 68%) as a white solid.

M. p. = 203−204 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ =13.06 (s, 1H), 9.33 (d, *J* = 1.6 Hz, 1H), 8.03 (d, *J* = 8.1 Hz, 2H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.59–7.52 (m, 1H), 7.52–7.46 (m, 2H), 7.33 (dd, *J* = 8.2, 1.6 Hz, 1H), 4.46 (td, *J* = 9.5, 1.1 Hz, 2H), 4.24 (td, J = 9.6, 1.1 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.3 (C_q), 163.9 (C_q), 140.6 (C_q), 134.4 (C_q), 132.2 (CH), 129.9 (CH), 128.7 (CH), 127.7 (CH), 125.3 (CH), 123.2 (CH), 118.2 (C_q), 116.7 (C_q), 115.8 (C_q), 66.7 (CH_2), 54.9 (CH_2). **IR** (ATR): 3065, 3025, 1677, 1616, 1579, 1414, 1289, 1240, 1059, 693 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 292 (5) [M+H^+], 291 (25) [M^+], 214 (35), 171 (15), 115 (10), 105 (100), 77 (60). **HR-MS**: (ESI) *m/z* calcd for $C_{17}H_{14}N_3O_2$ [M+H^+] 292.1081, found 292.1079.



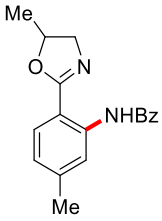
***N*-[4-Chloro-2-(4,5-dihydrooxazol-2-yl)phenyl]benzamide (133va)**: The general procedure **E** was followed using oxazoline **130v** (86 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **133va** (101 mg, 67%) as a white solid.

M. p. = 140−141 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.88 (s, 1H), 8.90 (d, *J* = 9.0 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 2.6 Hz, 1H), 7.54–7.45 (m, 1H), 7.49–7.40 (m, 2H), 7.39 (dd, *J* = 9.0, 2.6 Hz, 1H), 4.34 (td, *J* = 9.4, 1.0 Hz, 2H), 4.12 (td, *J* = 9.4, 1.0 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 165.8 (C_q), 163.8 (C_q), 138.6 (C_q), 134.8 (C_q), 132.2 (CH), 131.7 (CH), 128.8 (CH), 128.5 (CH), 127.6 (CH), 127.2 (C_q), 121.0 (CH), 114.7 (C_q), 66.3 (CH_2), 54.6 (CH_2). **IR** (ATR): 3048, 2969, 1666, 1615, 1579, 1474, 1230, 1057, 950, 693 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 300 (30) [M^+] (^{35}Cl), 307 (5), 223 (30), 180 (15), 124 (15), 105 (100). **HR-MS** (EI) *m/z* calcd for $C_{16}H_{13}{}^{35}ClN_2O_2$ [M^+] 300.0666, found 300.0655.



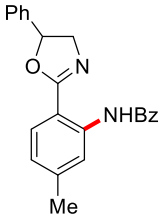
***N*-[2-(4,5-Dihydrooxazol-2-yl)-4-(trifluoromethyl)phenyl]benzamide (133wa)**: The general procedure **E** was followed using oxazoline **130w** (108 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 7:1) yielded **133wa** (108 mg, 65%) as a white solid.

M. p. = 184–187 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 13.17 (s, 1H), 9.11 (dt, *J* = 8.9, 0.7 Hz, 1H), 8.19 (dt, *J* = 2.3, 0.6 Hz, 1H), 8.09 (d, *J* = 8.1 Hz, 2H), 7.75 (ddt, *J* = 8.9, 2.3, 0.6 1H), 7.64–7.45 (m, 3H), 4.48 (td, *J* = 9.1, 1.6 Hz, 2H), 4.26 (td, *J* = 9.1, 1.6 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.2 (C_q), 164.0 (C_q), 142.8 (C_q), 134.7 (C_q), 132.0 (CH), 129.2 (q, $^3J_{C\text{-}F}$ = 3.4 Hz, CH), 128.6 (CH), 127.7 (CH), 126.5 (q, $^3J_{C\text{-}F}$ = 4.0 Hz, CH), 124.9 (q, $^1J_{C\text{-}F}$ = 271.3 Hz, C_q), 124.2 (q, $^2J_{C\text{-}F}$ = 33.4 Hz, C_q), 119.9 (CH), 113.4 (C_q), 66.6 (CH_2), 54.8 (CH_2). **^{19}F NMR** (282 MHz, $CDCl_3$) δ = -62.2 (s). IR (ATR): 3013, 1627, 1308, 1237, 1107, 1082, 1058, 952, 695 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 334 (38) [M^+], 257 (57), 214 (21), 158 (10), 105 (100), 77 (64). **HR-MS** (EI) *m/z* calcd for $C_{17}H_{13}N_2O_2F_3$ [M^+]: 334.0929, found: 334.0923.



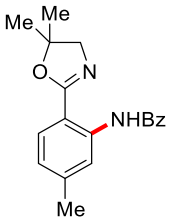
***N*-[5-Methyl-2-(5-methyl-4,5-dihydrooxazol-2-yl)phenyl]benzamide (133xa)**: The general procedure **E** was followed using oxazoline **130x** (88 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 8:1) yielded **133xa** (125 mg, 85%) as a white solid.

M. p. = 126–128 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 13.06 (s, 1H), 8.83 (dq, *J* = 1.1, 0.6 Hz, 1H), 8.16–8.06 (m, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.59–7.45 (m, 3H), 6.97–6.88 (m, 1H), 4.81 (ddq, *J* = 9.4, 7.4, 6.2 Hz, 1H), 4.26 (dd, *J* = 14.2, 9.4 Hz, 1H), 3.73 (dd, *J* = 14.2, 7.4 Hz, 1H), 2.44 (s, 3H), 1.44 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.2 (C_q), 164.5 (C_q), 143.5 (C_q), 140.2 (C_q), 135.6 (C_q), 131.7 (CH), 129.3 (CH), 128.7 (CH), 127.9 (CH), 123.4 (CH), 120.5 (CH), 111.4 (C_q), 75.0 (CH), 61.3 (CH_2), 22.2 (CH_3), 21.1 (CH_3). **IR** (ATR): 3063, 2974, 1622, 1585, 1295, 1243, 1062, 1049, 696, 677 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 294 (22) [M^+], 217 (100), 160 (29), 105 (34), 77 (44). **HR-MS** (EI) *m/z* calcd for $C_{18}H_{18}N_2O_2$ [M^+]: 294.1368, found: 294.1370.



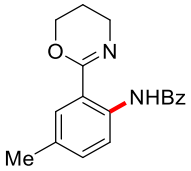
***N*-[5-Methyl-2-(5-phenyl-4,5-dihydrooxazol-2-yl)phenyl]benzamide (133ya)**: The general procedure **E** was followed using oxazoline **130y** (119 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 8:1) yielded **133ya** (131 mg, 74%) as a white solid.

M. p. = 131–133 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.99 (s, 1H), 8.88 (t, *J* = 1.1 Hz, 1H), 8.16–8.06 (m, 2H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.61–7.45 (m, 3H), 7.45–7.30 (m, 5H), 6.96 (ddd, *J* = 8.0, 1.7, 0.8 Hz, 1H), 5.64 (dd, *J* = 10.1, 7.7 Hz, 1H), 4.60 (dd, *J* = 14.5, 10.1 Hz, 1H), 4.13 (dd, *J* = 14.5, 7.7 Hz, 1H), 2.46 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.2 (C_q), 164.6 (C_q), 143.8 (C_q), 140.7 (C_q), 140.4 (C_q), 135.5 (C_q), 131.7 (CH), 129.5 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 127.9 (CH), 125.8 (CH), 123.6 (CH), 120.6 (CH), 111.0 (C_q), 79.6 (CH), 62.9 (CH_2), 22.3 (CH_3). **IR** (ATR): 3066, 2965, 1618, 1294, 1055, 759, 707, 694, 677 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 356 (40) [M^+], 279 (45), 238 (25), 160 (61), 119 (27), 105 (99), 77 (100). **HR-MS** (EI) *m/z* calcd for $C_{23}H_{20}N_2O_2$ [M^+]: 356.1525, found: 356.1533.



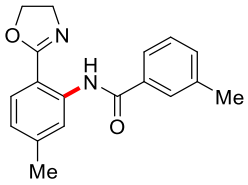
***N*-[2-(5,5-Dimethyl-4,5-dihydrooxazol-2-yl)-5-methylphenyl]benzamide (133za)**: The general procedure **E** was followed using oxazoline **130z** (95 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 8:1) yielded **133za** (132 mg, 86%) as a white solid.

M. p. = 103–105 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 13.13 (s, 1H), 8.87–8.81 (m, 1H), 8.16–8.07 (m, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.58–7.45 (m, 3H), 6.93 (ddd, *J* = 8.0, 1.7, 0.8 Hz, 1H), 3.89 (s, 2H), 2.44 (s, 3H), 1.50 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.1 (C_q), 163.9 (C_q), 143.3 (C_q), 140.2 (C_q), 135.6 (C_q), 131.6 (CH), 129.2 (CH), 128.6 (CH), 127.9 (CH), 123.3 (CH), 120.4 (CH), 111.7 (C_q), 82.9 (C_q), 66.6 (CH_2), 27.4 (CH_3), 22.2 (CH_3). **IR** (ATR): 3065, 2974, 2873, 1620, 1583, 1298, 1059, 695, 677 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 308 (53) [M^+], 275 (21), 231 (100), 160 (93), 134 (14), 105 (72), 77 (69), 51 (9). **HR-MS** (ESI) *m/z* calcd for $C_{19}H_{21}N_2O_2$ [$M+H^+$]: 309.1598, found: 309.1598.



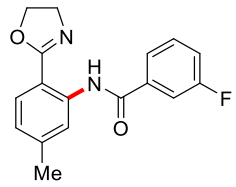
***N*-[2-(5,6-Dihydro-4*H*-1,3-oxazin-2-yl)-4-methylphenyl]benzamide (133aaa)**: The general procedure **E** was followed using oxazine **130aa** (88 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 8:1) yielded **133aaa** (97 mg, 66%) as a white solid.

M. p. = 127–129 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 13.87 (s, 1H), 8.81 (d, *J* = 8.5 Hz, 1H), 8.07–7.97 (m, 2H), 7.72 (d, *J* = 2.1 Hz, 1H), 7.58–7.41 (m, 3H), 7.27 (dd, *J* = 8.5, 2.1 Hz, 1H), 4.42 (t, *J* = 5.4 Hz, 2H), 3.73 (t, *J* = 5.9 Hz, 2H), 2.34 (s, 3H), 2.04 (tt, *J* = 5.9, 5.4 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 165.7 (C_q), 157.1 (C_q), 137.9 (C_q), 136.1 (C_q), 132.3 (CH), 131.5 (C_q), 131.4 (CH), 128.6 (CH), 128.4 (CH), 127.6 (CH), 120.1 (CH), 118.3 (C_q), 65.5 (CH_2), 42.1 (CH_2), 21.7 (CH_2), 21.0 (CH_3). **IR** (ATR): 2853, 1641, 1595, 1525, 1349, 1237, 822, 701, 543 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 294 (54) [M^+], 217 (100), 189 (11), 160 (61), 105 (52), 77 (61). **HR-MS** (ESI) *m/z* calcd for $C_{18}H_{19}N_2O_2$ [M+H^+]: 295.1441, found: 295.1444.



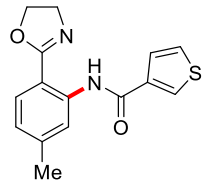
***N*-(2-(4,5-dihydrooxazol-2-yl)-5-methylphenyl)-3-methylbenzamide(133ib)**: The general procedure **E** was followed using oxazine **130i** (88 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132b** (106 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 8:1) yielded **133ib** (63 mg, 43%) as a white solid.

M. p. = 145−146 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 12.95 (s, 1H), 8.80 (s, 1H), 7.93 – 7.83 (m, 2H), 7.74 (d, J = 8.0 Hz, 1H), 7.40 – 7.29 (m, 2H), 6.89 (ddt, J = 8.0, 1.5, 0.7 Hz, 1H), 4.35 (td, J = 9.4, 1.3 Hz, 2H), 4.13 (td, J = 9.4, 1.3 Hz, 2H), 2.42 (s, 3H), 2.41 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 166.1 (C_q), 164.9 (C_q), 143.3 (C_q), 140.0 (C_q), 138.2 (C_q), 135.2 (C_q), 132.2 (CH), 129.1 (CH), 128.5 (CH), 128.4 (CH), 124.7 (CH), 123.2 (CH), 120.2 (CH), 110.9 (C_q), 66.1 (CH_2), 54.5 (CH_2), 22.0 (CH_3), 21.4 (CH_3). **IR (neat)**: 3066, 2914, 1681, 1619, 1583, 1362, 1299, 1103, 802, 765, 500 cm^{-1}. **MS** (EI) m/z (relative intensity) 294 (40) [M^+], 277 (12), 250 (5), 203 (100), 160 (30), 119 (40). **HR-MS** (EI) m/z calcd for $C_{18}H_{18}N_2O_2$ [M^+] 294.1368, found 294.1361.



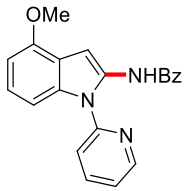
***N*-[2-(4,5-Dihydrooxazol-2-yl)-5-methylphenyl]-3-fluorobenzamide (133ic)**: The general procedure **E** was followed using oxazoline **133i** (81mg, 0.50 mmol, 1.0 equiv), dioxazolone **132c** (109 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **133ic** (98 mg, 66%) as a white solid.

M. p. = 163−164 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 13.03 (s, 1H), 8.76 (s, 1H), 7.88–7.84 (m, 1H), 7.81–7.73 (m, 2H), 7.44 (td, *J* = 8.0, 5.6 Hz, 1H), 7.23–7.17 (m, 1H), 6.93–6.90 (m, 1H), 4.41–4.33 (m, 2H), 4.19–4.12 (m, 2H), 2.41 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 165.0 (C_q), 164.5 (d, $^4J_{C\text{-}F}$ = 2.6 Hz, C_q), 162.8 (d, $^1J_{C\text{-}F}$ = 246.8 Hz, C_q), 143.5 (C_q), 139.7 (C_q), 137.6 (d, $^3J_{C\text{-}F}$ = 6.8 Hz, C_q), 130.1 (d, $^3J_{C\text{-}F}$ = 7.9 Hz, CH), 129.1 (CH), 123.6 (CH), 123.3 (d, $^4J_{C\text{-}F}$ = 3.0 Hz, CH), 120.3 (CH), 118.5 (d, $^2J_{C\text{-}F}$ = 21.4 Hz, CH), 114.9 (d, $^2J_{C\text{-}F}$ = 23.0 Hz, CH), 111.0 (C_q), 66.2 (CH_2), 54.5 (CH_2), 22.1 (CH_3). **^{19}F-NMR** (282 MHz, $CDCl_3$) δ = –112.1 (m). **IR** (ATR): 3055, 2915, 2881, 1624, 1588, 1420, 1359, 1297, 1059, 726 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 298 (70) [M^+], 281 (15), 267 (10), 203 (100), 160 (70), 123 (40). **HR-MS** (EI) *m/z* calcd for $C_{17}H_{15}FN_2O_2$ [M^+] 298.1118, found 294.1121.



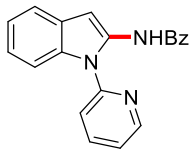
N-(2-(4,5-dihydrooxazol-2-yl)-5-methylphenyl)thiophene-3-carboxamide(133id): The general procedure **E** was followed using oxazoline **130i** (81mg, 0.50 mmol, 1.0 equiv), dioxazolone **132d** (102 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %) and NaOAc (8.2 mg, 0.10 mmol, 20 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **133id** (51 mg, 36%) as a white solid.

M. p. = 168−169 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 13.02 (s, 1H), 8.68 (s, 1H), 7.76 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.51 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.10 (dd, *J* = 5.0, 3.8 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.4, 1H), 4.40–4.31 (m, 2H), 4. 18–4.11 (m, 2H), 2.38 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 164.9 (C_q), 160.6 (C_q), 143.4 (C_q), 141.2 (C_q), 139.7 (C_q), 130.8 (CH), 129.0 (CH), 128.4 (CH), 127.7 (CH), 123.2 (CH), 120.1 (CH), 110.6 (C_q), 66.1 (CH_2), 54.5 (CH_2), 22.0 (CH_3). **IR (neat)**: 3113, 2959, 1621, 1587, 1553, 1413, 1352, 1298, 1060, 725, 509, 456 cm^{-1}. **MS** (EI) m/z (relative intensity) 286 (90) [M^+], 269 (30), 255 (20), 225 (30), 203 (70), 160 (50), 111 (100). **HR-MS** (EI) m/z calcd for $C_{15}H_{14}N_2O_2S$ [M^+] 286.0776, found 286.0765.



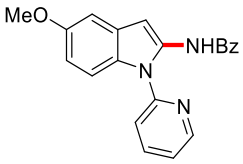
***N*-[4-Methoxy-1-(pyridin-2-yl)-1*H*-indol-2-yl]benzamide (154aa)**: The general procedure **F** was followed using indole **102a** (112 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (5.9 mg, 0.0125 mmol, 2.5 mol %), $AgSbF_6$ (8.6 mg, 0.025 mmol, 5.0 mol %) and NaOAc (2.1 mg, 0.025 mmol, 5.0 mol %) at 70 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) yielded **154aa** (165 mg, 96%) as a pale yellow solid.

M. p. = 152–154 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 11.75 (s, 1H), 8.61 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.97–7.86 (m, 3H), 7.75 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.58–7.45 (m, 3H), 7.41 (s, 1H), 7.30–7.18 (m, 2H), 7.11 (t, *J* = 8.1 Hz, 1H), 6.66 (dd, *J* = 7.9, 0.6 Hz, 1H), 3.98 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 163.5 (C_q), 153.4 (C_q), 152.2 (C_q), 148.2 (CH), 139.5 (CH), 134.5 (C_q), 133.5 (C_q), 133.2 (C_q), 131.9 (CH), 128.8 (CH), 127.1 (CH), 122.7 (CH), 120.9 (CH), 119.9 (C_q), 118.2 (CH), 104.0 (CH), 102.7 (CH), 91.2 (CH), 55.7 (CH_3). **IR** (ATR): 3057, 2954, 1666, 1538, 1470, 1437, 1250, 1090, 764, 686. **MS** (EI) *m/z* (relative intensity) 343 (69) [M^+], 281 (6), 238 (27), 207 (20), 169 (7), 105 (100), 77 (40), 44 (11). **HR-MS** (ESI) *m/z* calcd for $C_{21}H_{18}N_3O_2$ [M+H^+]: 344.1394, found: 344.1394.



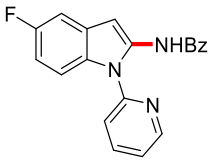
***N*-[1-(Pyridin-2-yl)-1*H*-indol-2-yl]benzamide (154ba)**: The general procedure **F** was followed using indole substrate **102b** (97 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (5.9 mg, 0.0125 mmol, 2.5 mol %), $AgSbF_6$ (8.6 mg, 0.025 mmol, 5.0 mol %) and NaOAc (2.1 mg, 0.025 mmol, 5.0 mol %) at 70 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) yielded **154ba** (150 mg, 94%) as a pale yellow solid.

M. p. = 101−102 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 11.88 (s, 1H), 8.59 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.95–7.91 (m, 2H), 7.88 (ddd, *J* = 8.3, 7.4, 1.9 Hz, 1H), 7.73 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.63–7.60 (m, 1H), 7.59–7.56 (m, 1H), 7.55–7.51 (m, 1H), 7.50–7.45 (m, 2H), 7.31 (s, 1H), 7.26–7.14 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 163.5 (C_q), 151.9 (C_q), 148.1 (CH), 139.4 (CH), 134.8 (C_q), 134.1 (C_q), 131.8 (CH), 131.9 (C_q), 129.5 (C_q), 128.7 (CH), 126.9 (CH), 122.0 (CH), 121.7 (CH), 120.7 (CH), 120.5 (CH), 117.8 (CH), 110.4 (CH), 93.6 (CH). **IR** (ATR): 3199, 3061, 3010, 1672, 1586, 1570, 1528, 1328, 789, 777 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 313 (90) [M^+], 285 (5), 208 (20), 181 (30), 105 (100), 77 (60). **HR-MS** (EI) *m/z* calcd for $C_{20}H_{15}N_3O$ [M^+] 313.1215, found 313.1207.



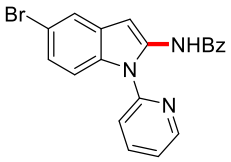
***N*-[5-Methoxy-1-(pyridin-2-yl)-1*H*-indol-2-yl]benzamide (154ca)**: The general procedure **F** was followed using indole substrate **102c** (112 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (5.9 mg, 0.0125 mmol, 2.5 mol %), $AgSbF_6$ (8.6 mg, 0.025 mmol, 5.0 mol %) and NaOAc (2.1 mg, 0.025 mmol, 5.0 mol %) at 70 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **154ca** (168 mg, 98%) as a pale yellow solid.

M. p. = 151−152 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 12.00 (s, 1H), 8.55 (dd, *J* = 5.0, 1.6 Hz, 1H), 7.91 (ddd, *J* = 7.0, 1.9, 1.0 Hz, 2H), 7.91–7.78 (m, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.55–7.39 (m, 4H), 7.23 (s, 1H), 7.24–7.13 (m, 1H), 7.06 (d, *J* = 2.5 Hz, 1H), 6.77 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.84 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 163.5 (C_q), 155.5 (C_q), 152.1 (C_q), 147.9 (CH), 139.3 (CH), 135.4 (C_q), 134.1 (C_q), 131.8 (CH), 130.5 (C_q), 128.7 (CH), 126.9 (CH), 126.4 (C_q), 120.3 (CH), 117.2 (CH), 111.3 (CH), 110.5 (CH), 103.0 (CH), 93.5 (CH), 55.6 (CH_3). **IR** (ATR): 3192, 3062, 2829, 1668, 1586, 1570, 1467, 1280, 776, 689 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 344 (20) [M+H$^+$], 343 (70) [M$^+$], 303 (5), 238 (30), 211 (15), 198 (20), 105 (100). **HR-MS** (EI) *m/z* calcd for $C_{20}H_{17}N_3O_2$ [M$^+$] 343.1321, found 343.1328.



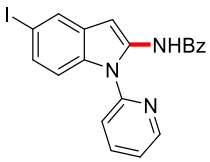
***N*-[5-Fluoro-1-(pyridin-2-yl)-1*H*-indol-2-yl]benzamide (154da)**: The general procedure **F** was followed using indole substrate **102d** (106 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (5.9 mg, 0.0125 mmol, 2.5 mol %), $AgSbF_6$ (8.6 mg, 0.025 mmol, 5.0 mol %) and NaOAc (2.1 mg, 0.025 mmol, 5.0 mol %) at 70 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) yielded **154da** (154 mg, 93%) as a pale yellow solid.

M. p. = 148−149 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 11.87 (s, 1H), 8.58–8.56 (m, 1H), 7.94–7.83 (m, 3H), 7.63 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.56–7.39 (m, 4H), 7.28–7.16 (m, 3H), 6.83 (td, *J* = 9.0, 2.6 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 163.6 (C_q), 158.9 (d, $^1J_{C\text{-}F}$ = 237.1 Hz, C_q), 151.7 (C_q), 148.1 (CH), 139.5 (CH), 136.2 (C_q), 133.9 (C_q), 131.9 (CH), 130.4 (d, $^3J_{C\text{-}F}$ = 10.5 Hz, C_q), 128.7 (CH), 128.1 (C_q), 126.9 (CH), 120.8 (CH), 117.5 (CH), 111.2 (d, $^3J_{C\text{-}F}$ = 9.4 Hz, CH), 109.2 (d, $^2J_{C\text{-}F}$ = 25.6 Hz, CH), 105.8 (d, $^2J_{C\text{-}F}$ = 24.1 Hz, CH), 93.3 (d, $^4J_{C\text{-}F}$ = 4.1 Hz, CH). **^{19}F-NMR** (282 MHz, $CDCl_3$) δ = –121.7 (m). IR (ATR): 3217, 3053, 1676, 1587, 1471, 1295, 1130, 1103, 840, 697 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 332 (20) [M+H$^+$], 331 (100) [M$^+$], 303 (5), 226 (20), 199 (30), 105 (100), 77 (60). **HR-MS** (EI) *m/z* calcd for $C_{20}H_{14}FN_3O$ [M$^+$] 331.1121, found 331.1124.



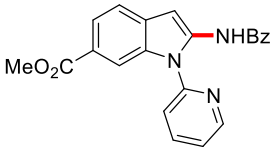
***N*-[5-Bromo-1-(pyridin-2-yl)-1*H*-indol-2-yl]benzamide (154ea)**: The general procedure **F** was followed using indole substrate **102e** (136 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (5.9 mg, 0.0125 mmol, 2.5 mol %), $AgSbF_6$ (8.6 mg, 0.025 mmol, 5.0 mol %) and NaOAc (2.1 mg, 0.025 mmol, 5.0 mol %) at 70 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) yielded **154ea** (186 mg, 95%) as a pale yellow solid.

M. p. = 140−141 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 11.81 (s, 1H), 8.59 (ddd, J = 5.0, 2.0, 0.8 Hz, 1H), 7.94–7.84 (m, 3H), 7.67–7.59 (m, 2H), 7.56–7.43 (m, 3H), 7.37 (d, J = 8.7 Hz, 1H), 7.29–7.23 (m, 1H), 7.21–7.15 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 163.6 (C_q), 151.5 (C_q), 148.2 (CH), 139.6 (CH), 135.8 (C_q), 133.9 (C_q), 132.0 (CH), 131.3 (C_q), 130.5 (C_q), 128.7 (CH), 127.0 (CH), 124.2 (CH), 122.9 (CH), 121.1 (CH), 117.7 (CH), 115.0 (C_q), 111.8 (CH), 92.7 (CH). **IR** (ATR): 3186, 3053, 3023, 1667, 1583, 1440, 1290, 1206, 872, 783, 637, 402 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 393 (56) [M^+] (^{81}Br), 391 (55) [M^+] (^{79}Br), 363 (5) (^{79}Br), 288 (10) (^{81}Br), 259 (10) (^{79}Br), 206 (20), 105 (100), 77 (60). **HR-MS** (EI) *m/z* calcd for $C_{20}H_{14}{}^{79}BrN_3O$ [M^+] 391.0320, found 391.0310.



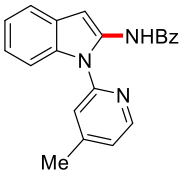
***N*-[5-Iodo-1-(pyridin-2-yl)-1*H*-indol-2-yl]benzamide (154fa)**: The general procedure **F** was followed using indole substrate **102f** (160 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (5.9 mg, 0.0125 mmol, 2.5 mol %), $AgSbF_6$ (8.6 mg, 0.025 mmol, 5.0 mol %) and NaOAc (2.1 mg, 0.025 mmol, 5.0 mol %) at 70 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) yielded **154fa** (180 mg, 82%) as a pale yellow solid.

M. p. = 159−160 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 11.80 (s, 1H), 8. 61–8.59 (m, 1H), 7.94–7.84 (m, 4H), 7.63 (dt, J = 8.3, 0.9 Hz, 1H), 7.56–7.43 (m, 3H), 7.39–7.34 (m, 1H), 7.31–7.23 (m, 2H), 7.17 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 163.6 (C_q), 151.5 (C_q), 148.2 (CH), 139.6 (CH), 135.4 (C_q), 133.9 (C_q), 132.0 (CH), 131.9 (C_q), 131.0 (C_q), 129.9 (CH), 129.1 (CH), 128.8 (CH), 127.0 (CH), 121.1 (CH), 117.8 (CH), 112.3 (CH), 92.5 (CH), 85.5 (C_q). **IR** (ATR): 3169, 3060, 1667, 1583, 1529, 1455, 1257, 990, 792, 750 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 440 (20) [M+H^+], 439 (70) [M^+], 411 (5), 334 (10), 206 (20), 105 (100), 77 (60). **HR-MS** (EI) *m/z* calcd for $C_{20}H_{14}IN_3O$ [M^+] 439.0182, found 439.0188.



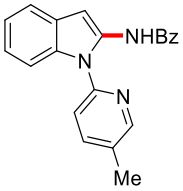
Methyl 2-benzamido-1-(pyridin-2-yl)-1*H*-indole-6-carboxylate (154ga): The general procedure **F** was followed using indole **102g** (126 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (5.9 mg, 0.0125 mmol, 2.5 mol %), $AgSbF_6$ (8.6 mg, 0.025 mmol, 5.0 mol %) and NaOAc (2.1 mg, 0.025 mmol, 5.0 mol %) at 70 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1 to 3:2) yielded **154ga** (169 mg, 91%) as an off-white solid.

M. p. = 180–183 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 11.95 (s, 1H), 8.67 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 8.32 (dt, *J* = 1.5, 0.8 Hz, 1H), 8.02 (ddd, *J* = 8.3, 7.5, 1.9 Hz, 1H), 7.97–7.87 (m, 3H), 7.82 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.63 (dd, *J* = 8.2, 0.6 Hz, 1H), 7.57 (ddt, *J* = 8.2, 6.4, 1.3 Hz, 1H), 7.52 (ddt, *J* = 8.2, 6.6, 1.4 Hz, 2H), 7.39–7.32 (m, 2H), 3.93 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 168.0 (C_q), 163.9 (C_q), 151.7 (C_q), 148.4 (CH), 140.1 (CH), 137.9 (C_q), 134.1 (C_q), 133.9 (C_q), 132.3 (CH), 131.5 (C_q), 129.0 (CH), 127.3 (CH), 123.6 (CH), 123.4 (C_q), 121.5 (CH), 120.1 (CH), 118.5 (CH), 112.6 (CH), 93.9 (CH), 52.1 (CH_3). **IR** (ATR): 3059, 2952, 1703, 1673, 1530, 1436, 1262, 1219, 998, 786 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 371 (34) [M^+], 281 (17), 253 (8), 207 (54), 105 (100), 77 (30), 44 (18). **HR-MS** (ESI) *m/z* calcd for $C_{22}H_{18}N_3O_3$ [M+H^+]: 372.1343, found: 372.1332.



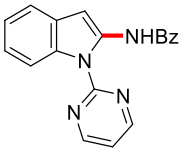
***N*-[1-(4-Methylpyridin-2-yl)-1*H*-indol-2-yl]benzamide (154ha)**: The general procedure **F** was followed using indole **102h** (104 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (5.9 mg, 0.0125 mmol, 2.5 mol %), $AgSbF_6$ (8.6 mg, 0.025 mmol, 5.0 mol %) and NaOAc (2.1 mg, 0.025 mmol, 5.0 mol %) at 70 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **154ha** (159 mg, 97%) as an off-white solid.

M. p. = 166–169 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 11.92 (s, 1H), 8.52–8.46 (m, 1H), 7.97–7.91 (m, 2H), 7.66–7.58 (m, 3H), 7.58–7.50 (m, 2H), 7.50–7.46 (m, 1H), 7.29 (s, 1H), 7.28–7.16 (m, 2H), 7.11 (ddd, *J* = 5.2, 1.5, 0.8 Hz, 1H), 2.49 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 163.8 (C_q), 152.2 (C_q), 151.4 (C_q), 147.9 (CH), 135.1 (C_q), 134.4 (C_q), 132.0 (CH), 132.0 (C_q), 129.8 (C_q), 128.9 (CH), 127.2 (CH), 122.2 (CH), 122.1 (CH), 121.7 (CH), 120.8 (CH), 118.6 (CH), 110.7 (CH), 93.6 (CH), 21.6 (CH_3). **IR** (ATR): 3228, 3044, 1672, 1523, 1459, 1259, 805, 685, 636, 447 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 327 (60) [M^+], 222 (26), 195 (26), 105 (100), 77 (41), 44 (33). **HR-MS** (ESI) *m/z* calcd for $C_{21}H_{18}N_3O$ [M+H^+]: 328.1444, found: 328.1447.



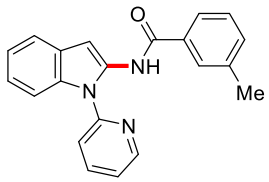
***N*-[1-(5-Methylpyridin-2-yl)-1*H*-indol-2-yl]benzamide (154ia)**: The general procedure **F** was followed using indole **102i** (104 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (5.9 mg, 0.0125 mmol, 2.5 mol %), $AgSbF_6$ (8.6 mg, 0.025 mmol, 5.0 mol %) and NaOAc (2.1 mg, 0.025 mmol, 5.0 mol %) at 70 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **154ia** (151 mg, 92%) as a pale yellow solid.

M. p. = 171–173 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 11.80 (s, 1H), 8.45 (dp, *J* = 2.3, 0.8 Hz, 1H), 8.00–7.86 (m, 2H), 7.75 (ddd, *J* = 8.4, 2.4, 0.7 Hz, 1H), 7.67 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.65–7.61 (m, 1H), 7.60–7.47 (m, 4H), 7.28 (t, *J* = 0.5 Hz, 1H), 7.24–7.13 (m, 2H), 2.44 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 163.6 (C_q), 149.9 (C_q), 148.2 (CH), 140.1 (CH), 134.9 (C_q), 134.4 (C_q), 132.0 (C_q), 131.9 (CH), 130.7 (C_q), 129.6 (C_q), 128.8 (CH), 127.2 (CH), 121.9 (CH), 121.7 (CH), 120.7 (CH), 117.6 (CH), 110.5 (CH), 93.5 (CH), 18.2 (CH_3). **IR** (ATR): 3183, 3049, 1683, 1539, 1477, 1455, 783, 690, 650, 637 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 327 (60) [M^+], 281 (24), 253 (13), 207 (76), 105 (100), 77 (35), 44 (22). **HR-MS** (ESI) *m/z* calcd for $C_{21}H_{18}N_3O$ [$M+H^+$]: 328.1444, found: 328.1444.



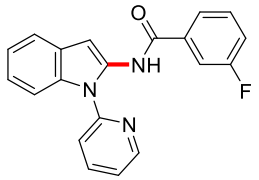
***N*-[1-(Pyrimidin-2-yl)-1*H*-indol-2-yl]benzamide (154ja)**: The general procedure **F** was followed using indole substrate **102j** (98 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (5.9 mg, 0.0125 mmol, 2.5 mol %), $AgSbF_6$ (8.6 mg, 0.025 mmol, 5.0 mol %) and NaOAc (2.1 mg, 0.025 mmol, 5.0 mol %) at 70 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **154ja** (148 mg, 94%) as a pale yellow solid.

M. p. = 137−138 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 12.99 (s, 1H), 8.63–8.59 (m, 1H), 8.57–8.55 (m, 2H), 7.94–7.87 (m, 2H), 7.55–7.41 (m, 4H), 7.37 (s, 1H), 7.17 (pd, *J* = 7.2, 1.5 Hz, 2H), 6.95 (t, *J* = 4.8 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 163.5 (C_q), 158.6 (C_q), 157.3 (CH), 135.5 (C_q), 134.4 (C_q), 132.5 (C_q), 131.7 (CH), 129.9 (C_q), 128.7 (CH), 126.9 (CH), 123.0 (CH), 122.4 (CH), 119.7 (CH), 116.5 (CH), 115.9 (CH), 95.6 (CH). **IR** (ATR): 3015, 1667, 1587, 1492, 1348, 1253, 791, 703, 588, 444 cm^{-1}. **MS** (EI) *m/z* (relative intensity), 315 (5) [$M+H^+$], 314 (40) [M^+], 231 (10), 210 (20), 105 (100). **HR-MS** (EI) *m/z* calcd for $C_{19}H_{14}N_4O$ [M^+] 314.1168, found 314.1165.



3-Methyl-*N*-[1-(pyridin-2-yl)-1*H*-indol-2-yl]benzamide (154bb): The general procedure **F** was followed using indole substrate **102b** (97 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132b** (106 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (5.9 mg, 0.0125 mmol, 2.5 mol %), $AgSbF_6$ (8.6 mg, 0.025 mmol, 5.0 mol %) and NaOAc (2.1 mg, 0.025 mmol, 5.0 mol %) at 70 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) yielded **154bb** (160 mg, 98%) as a pale yellow solid.

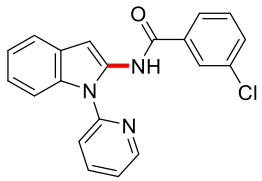
M. p. = 112−113 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 11.88 (s, 1H), 8.59–8.57 (m, 1H), 7.88 (ddd, J = 8.4, 7.4, 2.0 Hz, 1H), 7.77–7.67 (m, 3H), 7.64–7.54 (m, 2H), 7.41–7.28 (m, 3H), 7.27–7.12 (m, 3H), 2.43 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 163.7 (C_q), 151.9 (C_q), 147.9 (CH), 139.3 (CH), 138.5 (C_q) 134.8 (C_q), 134.0 (C_q), 132.6 (CH), 131.7 (C_q), 129.5 (C_q), 128.5 (CH), 127.8 (CH), 123.8 (CH), 121.9 (CH), 121.6 (CH), 120.7 (CH), 120.5 (CH), 117.8 (CH), 110.4 (CH), 93.5 (CH), 21.4 (CH_3). **IR** (ATR): 3180, 3047, 1687, 1570, 1456, 1342, 1210, 772, 733, 688 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 328 (20) [M+H$^+$], 327 (100) [M$^+$], 299 (10), 208 (20), 181 (35), 181 (35), 119 (100). **HR-MS** (EI) *m/z* calcd for $C_{21}H_{17}N_3O_2$ [M$^+$] 327.1372, found 327.1375.



3-Fluoro-*N*-[1-(pyridin-2-yl)-1*H*-indol-2-yl]benzamide (154bc): The general procedure **F** was followed using indole substrate **102b** (97 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132c** (109 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (5.9 mg, 0.0125 mmol, 2.5 mol %), $AgSbF_6$ (8.6 mg, 0.025 mmol, 5.0 mol %) and NaOAc (2.1 mg, 0.025 mmol, 5.0 mol %) at 100 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) yielded **154bc** (126 mg, 76%) as a pale yellow solid.

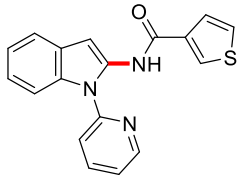
M. p. = 105−106 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 11.98 (s, 1H), 8.59 (dd, J = 5.0, 1.7 Hz, 1H), 7. 92–7.86 (m, 1H), 7.76–7.71 (m, 1H), 7.69–7.55 (m, 4H), 7.44 (td, J = 8.0, 5.6 Hz, 1H), 7.28–7.20 (m, 3H), 7.21–7.12 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 164.4 (d, $^1J_{C\text{-}F}$ = 247.9 Hz, C_q), 162.1 (d, $^4J_{C\text{-}F}$ = 2.7 Hz, C_q), 151.9 (C_q), 148.0 (CH), 139.5 (CH), 136.4 (d, $^3J_{C\text{-}F}$ = 6.9 Hz, C_q), 134.5 (C_q), 131.7 (C_q), 130.3 (d, $^3J_{C\text{-}F}$ = 7.9 Hz, CH), 129.4 (C_q), 122.4 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, CH), 122.1 (CH), 121.8 (CH), 120.7 (CH), 120.6 (CH), 118.8 (d, $^2J_{C\text{-}F}$ = 21.3 Hz, CH), 117.7 (CH), 114.3 (d, $^2J_{C\text{-}F}$ = 23.1 Hz, CH), 110.5 (CH), 93.8 (CH). **^{19}F-NMR** (282 MHz, $CDCl_3$) δ = –114.4. **IR** (ATR): 3057, 3022, 1685, 1583, 1540, 1322, 1208, 873, 712, 637 cm^{-1}. **MS** (EI) *m/z*

(relative intensity) 332 (30) [M+H$^+$], 331 (100) [M$^+$], 303 (10), 208 (50), 181 (50), 123 (70), 95 (40). **HR-MS** (EI) *m/z* calcd for $C_{20}H_{14}FN_3O$ [M$^+$] 331.1121, found 331.1134.



3-Chloro-*N*-[1-(pyridin-2-yl)-1*H*-indol-2-yl]benzamide (154be): The general procedure **F** was followed using indole substrate **102b** (97 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132e** (119 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (5.9 mg, 0.0125 mmol, 2.5 mol %), $AgSbF_6$ (8.6 mg, 0.025 mmol, 5.0 mol %) and NaOAc (2.1 mg, 0.025 mmol, 5.0 mol %) at 100 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) yielded **154be** (113 mg, 65%) as a pale yellow solid.

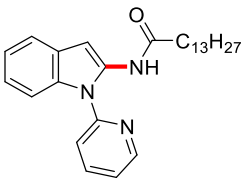
M. p. = 145−146 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.02 (s, 1H), 8.60 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.95–7.85 (m, 2H), 7.81–7.72 (m, 2H), 7.62–7.56 (m, 2H), 7.49 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.28–7.23 (m, 2H), 7.21–7.13 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 162.0 (C_q), 152.0 (C_q), 148.0 (CH), 139.5 (CH), 135.9 (C_q), 134.8 (C_q), 134.5 (C_q), 131.7 (C_q), 131.8 (CH), 130.0 (CH), 129.5 (C_q), 127.4 (CH), 125.1 (CH), 122.1 (CH), 121.9 (CH), 120.7 (CH), 120.7 (CH), 117.7 (CH), 110.6 (CH), 93.8 (CH). **IR** (ATR): 3055, 1689, 1569, 1545, 1341, 1259, 866, 733, 707, 671 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 347 (100) [M$^+$], 319 (10), 252 (10), 208 (70), 181 (70), 139 (85). **HR-MS** (EI) *m/z* calcd for $C_{20}H_{14}{}^{35}ClN_3O$ [M$^+$] 347.0825, found 347.0827.



***N*-[1-(Pyridin-2-yl)-1*H*-indol-2-yl]thiophene-3-carboxamide (154bd)**: The general procedure **F** was followed using indole substrate **102b** (97 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132d** (101 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (5.9 mg, 0.0125 mmol, 2.5 mol %), $AgSbF_6$ (8.6 mg, 0.025 mmol, 5.0 mol %) and NaOAc (2.1 mg, 0.025 mmol, 5.0 mol %) at 70 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) yielded **154bd** (153 mg, 96%) as a pale yellow solid.

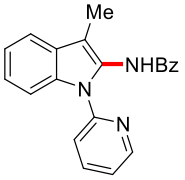
M. p. = 128−129 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 11.85 (s, 1H), 8.59 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.87 (ddd, *J* = 8.3, 7.4, 2.0 Hz, 1H), 7.70 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.62–7.53 (m, 3H), 7.50 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.25–7.19 (m, 2H), 7.19–7.12 (m, 2H), 7.09 (dd, *J* = 5.0, 3.7 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 158.1 (C_q), 151.8 (C_q), 148.0 (CH), 139.4 (CH), 139.1 (C_q), 134.3 (C_q), 131.7 (C_q), 130.6 (CH), 129.4 (C_q), 128.4 (CH), 127.8 (CH), 122.0 (CH), 121.7 (CH), 120.6 (CH), 120.5 (CH), 117.6 (CH), 110.5 (CH), 93.5

(CH). **IR** (ATR): 3148, 3071, 1639, 1568, 1531, 1455, 1362, 1321, 844, 777, 727 cm^{-1}. **MS** (EI) m/z (relative intensity), 320 (10) [M+H$^+$], 319 (30), 291 (10), 208 (70), 181 (70), 111 (100). **HR-MS** (EI) m/z calcd for $C_{18}H_{13}N_3OS$ [M$^+$] 319.0779, found 319.0782.



***N*-[1-(Pyridin-2-yl)-1*H*-indol-2-yl]tetradecanamide (154bf)**: The general procedure **F** was followed using indole substrate **102b** (97 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132f** (162 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (5.9 mg, 0.0125 mmol, 2.5 mol %), $AgSbF_6$ (8.6 mg, 0.025 mmol, 5.0 mol %) and NaOAc (2.1 mg, 0.025 mmol, 5.0 mol %) at 70 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 6:1) yielded **154bf** (205 mg, 98%) as a pale yellow solid.

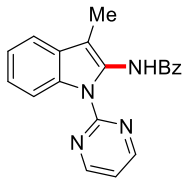
M. p. = 89−90 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 10.65 (s, 1H), 8.54 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.87 (td, *J* = 7.9, 1.9 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.60–7.46 (m, 2H), 7.28–7.06 (m, 4H), 2.37 (t, *J* = 7.3 Hz, 2H), 1.69 (p, *J* = 7.3 Hz, 2H), 1.36–1.19 (m, 20H), 0.93–0.82 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 170.0 (C_q), 151.7 (C_q), 148.2 (CH), 139.2 (CH), 134.2 (C_q), 131.6 (C_q), 129.4 (C_q), 121.8 (CH), 121.5 (CH), 120.7 (CH), 120.4 (CH), 118.1 (CH), 110.2 (CH), 93.4 (CH), 37.7 (CH_2), 31.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 25.3 (CH_2), 22.6 (CH_2), 14.0 (CH_3). **IR** (ATR): 3327, 3059, 2916, 2849, 1668, 1533, 1438, 1320, 1207, 738 cm^{-1}. **MS** (EI) *m/z* (relative intensity), 420 (10) [M+H$^+$], 419 (40) [M$^+$], 361 (5), 209 (100), 181 (70), 169 (10). **HR-MS** (ESI) *m/z* calcd for $C_{13}H_{38}N_3O$ [M+H$^+$] 420.3009, found 420.3002.



***N*-[3-Methyl-1-(pyridin-2-yl)-1*H*-indol-2-yl]benzamide (154ka)**: The general procedure **F** was followed using indole substrate **102k** (97 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (17 mg, 0.050 mmol, 10 mol %) and NaOAc (4.1 mg, 0.050 mmol, 10 mol %) at 100 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) yielded **154ka** (105 mg, 64%) as a pale yellow solid.

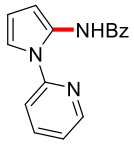
M. p. = 144−145 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 10.07 (s, 1H), 8.41–8.38 (m, 1H), 8.01–7.89 (m, 2H), 7.78 (td, *J* = 7.8, 1.9 Hz, 1H), 7.60–7.56 (m, 1H), 7.55–7.42 (m, 5H), 7.25–7.17 (m, 2H), 7.11 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H), 2.22 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 164.7 (C_q), 150.9 (C_q), 148.4 (CH), 138.7 (CH),

133.9 (C_q), 133.4 (C_q), 131.9 (CH), 128.9 (C_q), 128.6 (CH), 128.4 (C_q), 127.4 (CH), 122.7 (CH), 121.0 (CH), 120.8 (CH), 119.1 (CH), 119.0 (CH), 109.8 (CH), 107.9 (C_q), 9.2 (CH_3). **IR** (ATR): 3151, 1676, 1591, 1471, 1455, 1245, 1217, 894, 740, 691 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 328 (20) [M+H^+], 327 (100) [M^+], 222 (100), 207 (20), 195 (30), 169 (5). **HR-MS** (EI) *m/z* calcd for $C_{21}H_{17}N_3O_2$ [M^+] 327.1372, found 327.1379.



***N*-[3-Methyl-1-(pyrimidin-2-yl)-1*H*-indol-2-yl]benzamide (154la)**: The general procedure **F** was followed using indole **102l** (105 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (17 mg, 0.050 mmol, 10 mol %) and NaOAc (4.1 mg, 0.050 mmol, 10 mol %) at 100 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 8:2 to 6:4) yielded **154la** (106 mg, 65%) as a white solid.

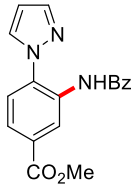
M. p. = 159–160 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 10.88 (s, 1H), 8.70 (d, *J* = 4.8 Hz, 2H), 8.56–8.46 (m, 1H), 7.99 (d, *J* = 6.9 Hz, 2H), 7.61–7.43 (m, 4H), 7.34–7.20 (m, 2H), 7.04 (t, *J* = 4.8 Hz, 1H), 2.31 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 158.1 (C_q), 157.9 (CH), 157.9 (C_q), 134.5 (C_q), 134.2 (C_q), 132.0 (CH), 130.0 (C_q), 129.1 (C_q), 128.8 (CH), 127.5 (CH), 123.6 (CH), 122.5 (CH), 118.5 (CH), 116.1 (CH), 114.9 (CH), 110.3 (C_q), 10.2 (CH_3). **IR** (ATR): 1673, 1562, 1503, 1429, 1272, 740, 710, 624 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 328 (58) [M^+], 223 (95), 207 (26), 153 (12) 105 (100), 77 (51), 44 (55). **HR-MS** (ESI) *m/z* calcd for $C_{20}H_{17}N_4O$ [M+H^+]: 329.1397, found: 329.1396.



***N*-[1-(Pyridin-2-yl)-1*H*-pyrrol-2-yl]benzamide (155aa)**: The general procedure **F** was followed using substrate **102m** (72 mg, 0.50 mmol, 1.0 equiv), dioxazolone **132a** (101 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (17 mg, 0.050 mmol, 10 mol %) and NaOAc (4.1 mg, 0.050 mmol, 10 mol %) at 100 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) yielded **155aa** (72 mg, 55%) as a pale yellow solid.

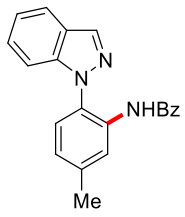
M. p. = 105−106 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 12.68 (s, 1H), 8.43 (ddd, *J* = 5.0, 1.9, 0.9 Hz, 1H), 7.98–7.92 (m, 2H), 7.80 (ddd, *J* = 8.5, 7.4, 1.9 Hz, 1H), 7.53–7.43 (m, 3H), 7.37 (dt, *J* = 8.5, 0.9 Hz, 1H), 7.14 (ddd, *J* = 7.4, 5.0, 0.9 Hz, 1H), 6.95 (dd, *J* = 3.6, 1.8 Hz, 1H), 6.91 (dd, J = 3.5, 1.8 Hz, 1H), 6.32 (td, J = 3.6, 0.5 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 162.8 (C_q), 153.4 (C_q), 146.8 (CH), 139.5 (CH), 134.7 (C_q), 131.4 (CH), 130.8 (C_q), 128.6 (CH), 126.9 (CH), 119.8 (CH), 113.4 (CH), 112.6 (CH), 110.8 (CH), 100.2

(CH). **IR** (ATR): 3162, 3057, 3024, 1662, 1572, 1539, 1490, 1469, 1283, 775 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 264 (20) [M+H^+], 263 (100) [M^+], 158 (100), 131 (20), 105 (100). **HR-MS** (EI) *m/z* calcd for $C_{16}H_{13}N_3O_2$ [M^+] 263.1059, found 263.1050.



Methyl 3-benzamido-4-(1*H*-pyrazol-1-yl)benzoate(156aa): The general procedure **F** was followed by using phenyl pyrozol **117a** (101 mg, 0.5 mmol), 3-phenyl-1,4,2-dioxazol-5-one (**132a**) (98 mg, 0.6 mmol, 1.2 equiv). Purification by column chromatography on silica gel (*n*-hexane /EtOAc 2:1) yielded **156aa** (135 mg, 84%) as a white solid.

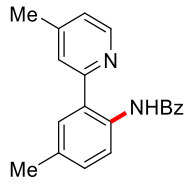
M. p. = 154−155 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 11.66 (s, 1H), 9.35 (d, *J* = 1.9 Hz, 1H), 7.96–7.90 (m, 3H), 7.85 (dd, *J* = 1.9, 0.6 Hz, 1H), 7.81 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.55–7.42 (m, 3H), 7.39 (d, *J* = 8.4 Hz, 1H), 6.50 (dd, *J* = 2.5, 1.9 Hz, 1H), 3.90 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 166.0 (C_q), 165.2 (C_q), 141.4 (CH), 134.4 (C_q), 131.9 (CH), 131.6 (C_q), 131.2 (C_q), 130.2 (CH), 129.2 (C_q), 128.6 (CH), 127.2 (CH), 125.2 (CH), 124.0 (CH), 121.3 (CH), 107.7 (CH), 52.2 (CH_3). **IR** (ATR): 3241, 3141, 2946, 1715, 1671, 1590, 1437, 1228, 763, 698 cm^{-1}. **MS** (EI) m/z (relative intensity), 322 (5) [M+H^+], 321 (40) [M^+], 290 (10), 189 (10), 105 (100). **HR-MS** (EI) m/z calcd for $C_{18}H_{15}N_3O_3$ [M^+] 321.1113, found 321.1109.



***N*-(2-(1*H*-indazol-1-yl)-5-methylphenyl)benzamide(156ba)**: The general procedure **F** was followed by using phenyl pyrozol **117b** (104 mg, 0.5 mmol), 3-phenyl-1,4,2-dioxazol-5-one **132a** (98 mg, 0.6 mmol, 1.2 equiv). Purification by column chromatography on silica gel (*n*-hexane /EtOAc 2:1) yielded **156ba** (154 mg, 94%) as a white solid.

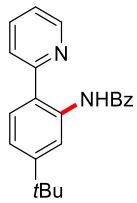
M. p. = 115−116 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 10.17 (s, 1H), 8.57–8.51 (m, 1H), 8.33 (d, *J* = 0.9 Hz, 1H), 7. 85–7.78 (m, 3H), 7.58 (dt, *J* = 8.6, 0.9 Hz, 1H), 7.51–7.36 (m, 5H), 7. 25–7.19 (m, 1H), 7. 10–7.06 (m, 1H), 2.49 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 164.8 (C_q), 139.8 (C_q), 138.4 (C_q), 135.5 (CH), 134.5 (C_q), 132.5 (C_q), 131.6 (CH), 128.5 (CH), 127.7 (CH), 126.9 (CH), 126.2 (C_q), 124.7 (CH), 124.1 (C_q), 123.9 (CH), 123.5 (CH), 121.9 (CH), 121.1 (CH), 110.6 (CH), 21.4 (CH_3). **IR** (ATR): 3342, 1673, 1592, 1531, 1497, 1464,

1414, 1347, 1299 cm^{-1}. **MS** (EI) m/z (relative intensity), 328 (20) [M +H^+], 327 (100) [M^+], 222 (30), 195 (10), 105 (100). **HR-MS** (EI) m/z calcd for $C_{21}H_{17}N_3O$ [M^+] 327.1372, found 327.1373.



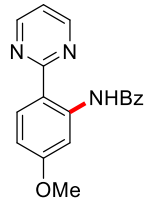
N-(4-methyl-2-(4-methylpyridin-2-yl)phenyl)benzamide (157aa): The general procedure **F** was followed by using phenyl pyridine **9a** (92 mg, 0.5 mmol), 3-phenyl-1,4,2-dioxazol-5-one **132a** (98 mg, 0.6 mmol, 1.2 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **157aa** (144 mg, 95%) as a white solid.

M. p. = 126−127 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 13.25 (s, 1H), 8.68 (d, J = 8.4 Hz, 1H), 8.47 (d, J = 5.1 Hz, 1H), 8.03–7.99 (m, 2H), 7.55 (s, 1H), 7.50–7.41 (m, 4H), 7.24 (dd, J = 8.5, 2.1 Hz, 1H), 7.05–7.02 (m, 1H), 2.38 (s, 3H), 2.37 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 165.1 (C_q), 157.9 (C_q), 148.9 (C_q), 146.8 (CH), 135.7 (C_q), 135.6 (C_q), 132.7 (C_q), 131.2 (CH), 130.5 (CH), 129.0 (CH), 128.4 (CH), 127.2 (CH), 125.5 (C_q), 123.5 (CH), 122.8 (CH), 121.6 (CH), 21.3 (CH_3), 20.9 (CH_3). **IR** (ATR): 2974, 1664, 1592, 1517, 1448, 1316, 1298, 1177, 819 cm^{-1}. **MS** (EI) m/z (relative intensity), 303 (10) [M+H^+], 302 (60) [M^+], 258 (10), 225 (100), 105 (60). **HR-MS** (EI) m/z calcd for $C_{20}H_{18}N_2O$ [M^+] 302.1419, found 302.1421.



***N*-(5-(*tert*-butyl)-2-(pyridin-2-yl)phenyl)benzamide(157ba)**: The general procedure **F** was followed by using phenyl pyridine **9b** (105 mg, 0.5 mmol), 3-phenyl-1,4,2-dioxazol-5-one **132a** (98 mg, 0.6 mmol, 1.2 equiv). Purification by column chromatography on silica gel (*n*-hexane /EtOAc 2:1) yielded **157ba** (152 mg, 92%) as a white solid.

M. p. = 111−112 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 13.54 (s, 1H), 9.00 (d, J = 2.1 Hz, 1H), 8.58 (dt, J = 4.9, 1.5 Hz, 1H), 8.12–8.03 (m, 2H), 7.76–7.67 (m, 2H), 7.64 (d, J = 8.3 Hz, 1H), 7. 51–7.45 (m, 3H), 7.26–7.12 (m, 2H), 1.42 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 165.4 (C_q), 157.9 (C_q), 153.5 (C_q), 146.9 (CH), 138.0 (C_q), 137.5 (CH), 135.7 (C_q), 131.3 (CH), 128.4 (CH), 128.1 (CH), 127.2 (CH), 122.3 (C_q), 122.2 (CH), 121.4 (CH), 120.5 (CH), 118.7 (CH), 34.9 (C_q), 31.1 (CH_3). **IR** (ATR): 2956, 1665, 1574, 1556, 1526, 1465, 1245, 703 cm^{-1}. **MS** (EI) m/z (relative intensity), 331 (10) [M +H^+], 330 (30) [M^+], 315 (10), 253 (30), 105 (100). **HR-MS** (EI) m/z calcd for $C_{20}H_{18}N_2O$ [M^+] 330.1732, found 330.1737.

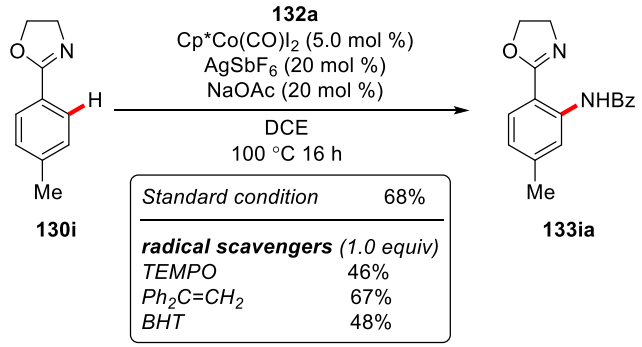


***N*-(5-Methoxy-2-(pyrimidin-2-yl)phenyl)benzamide(157ca)**: The general procedure **F** was followed by using phenyl pyrimidine **9c** (93 mg, 0.5 mmol), 3-phenyl-1,4,2-dioxazol-5-one **132a** (98 mg, 0.6 mmol, 1.2 equiv). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **157ca** (90 mg, 59%) as a white solid.

M. p. = 71−72 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 13.76 (s, 1H), 8.74 (d, *J* = 4.8, 2H), 8.65 (d, *J* = 2.7 Hz, 1H), 8.59 (d, *J* = 9.0 Hz, 1H), 8.13–8.01 (m, 2H), 7.61–7.41 (m, 3H), 7.11 (dd, *J* = 4.8, 0.5 Hz, 1H), 6.74 (dd, *J* = 9.0, 2.7 Hz, 1H), 3.92 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 166.0 (C_q), 164.9 (C_q), 162.7 (C_q), 156.2 (CH), 142.0 (C_q), 135.9 (C_q), 131.9 (CH), 131.6 (CH), 128.6 (CH), 127.4 (CH), 117.6 (CH), 115.4 (C_q), 110.5 (CH), 104.5 (CH), 55.5 (CH_3). **IR** (ATR): 3236, 3027, 2842, 2233, 1672, 1574, 1390, 1189 cm^{-1}. **MS** (EI) m/z (relative intensity), 306 (20) [M +H$^+$], 305 (100) [M $^+$], 228 (90), 155 (30), 105 (100). **HR-MS** (EI) m/z calcd for $C_{18}H_{15}N_3O_2$ [M $^+$] 305.1164, found 305.1166.

Reactions with Radical Scavengers:

(a) Radical Scavengers



Reaction with TEMPO

130i (81 mg, 0.50 mmol, 1.0 equiv), **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %), NaOAc (8.2 mg, 0.10 mmol, 20 mol %) and TEMPO (78 mg, 0.50 mmol, 1.0 equiv) were placed into a 25 mL Schlenk tube equipped with a septum under N_2 atmosphere. DCE (2.0 mL) was introduced *via* cannula. The reaction mixture was stirred at 100 °C for 16 h. After cooling to ambient temperature, the reaction mixture was dry loaded onto silica gel and purified by flash column chromatography (*n*-hexane/EtOAc = 7:1) to yield the product **133ia** (64 mg, 46%) as an off-white solid.

Reaction with 1,1-Diphenylethylene

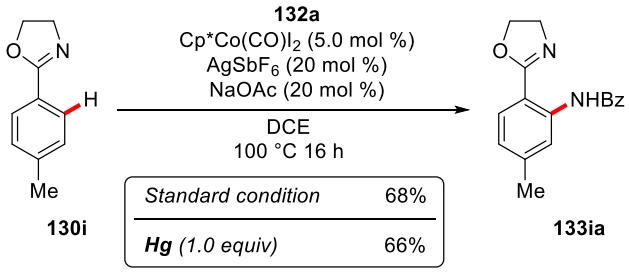
130i (81 mg, 0.50 mmol, 1.0 equiv), **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (11.9 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %), NaOAc (8.2 mg, 0.10 mmol, 20 mol %) and 1,1-diphenylethylene (90 mg, 0.50 mmol, 1.0 equiv) were placed into a 25 mL Schlenk tube equipped with a septum under N_2 atmosphere. DCE (2.0 mL) was introduced *via* cannula. The reaction mixture was stirred at 100 °C for 16 h. After cooling to ambient temperature, the reaction mixture was dry loaded onto silica gel and purified by flash column chromatography (*n*-hexane/EtOAc = 7:1) to yield the product **133ia** (95 mg, 67%) as a white solid.

Reaction with BHT

130i (81 mg, 0.50 mmol, 1.0 equiv), **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (12 mg, 0.025 mmol, 5 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %), NaOAc (8.2 mg, 0.10 mmol, 20 mol %) and 2,6-bis(1,1-dimethylethyl)-4-methylphenol (110 mg, 0.50 mmol, 1.0 equiv) were placed into a 25 mL Schlenk tube equipped with a septum under N_2 atmosphere. DCE (2.0 mL) was introduced *via* cannula. The reaction mixture was stirred at 100 °C for 16 h. After cooling to ambient temperature, the reaction mixture was dry loaded onto silica gel and purified by flash column chromatography (*n*-hexane/EtOAc = 7:1) to yield the product **133ia** (67 mg, 48%) as a white solid.

Mercury Test

(b) Mercury-test: Homogenous catalysis

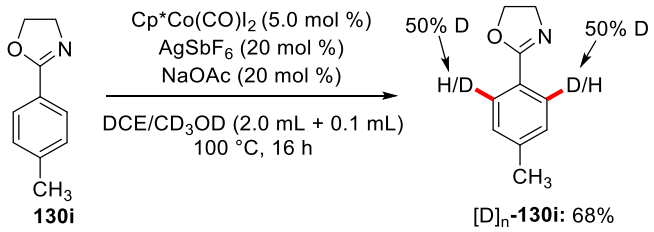


130i **133ia**

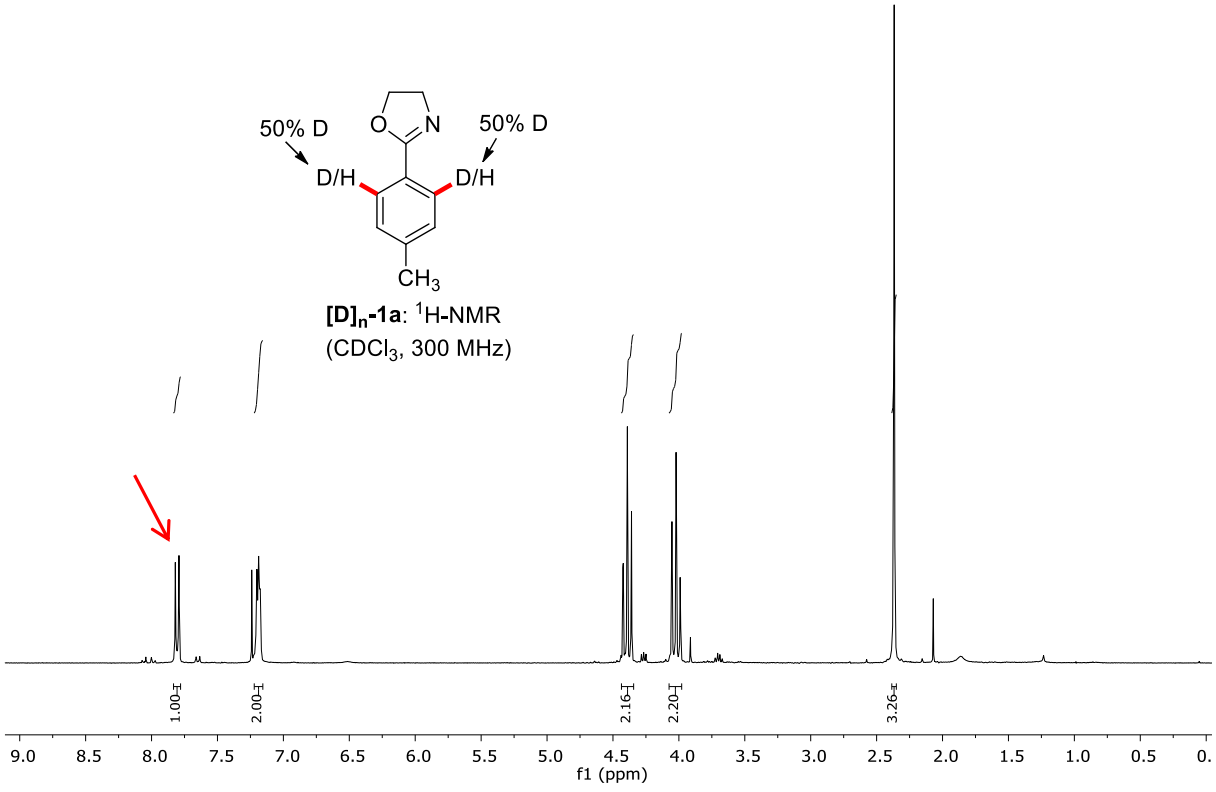
133i (81 mg, 0.50 mmol, 1.0 equiv), **132a** (98 mg, 0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (12 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.10 mmol, 20 mol %), and NaOAc (8.2 mg, 0.10 mmol, 20 mol %) were placed into a 25 mL Schlenk tube equipped with a septum under N_2 atmosphere. DCE (2.0 mL) was introduced *via* cannula. The reaction mixture was stirred at 100 °C for 2.5 min. (No detectable formation of **133ia** was observed by GC-MS analysis of an aliquot of the reaction mixture). Mercury (100 mg, 0.50 mmol, 1.0 equiv) was then added *via* syringe. The reaction mixture was stirred at 100 °C for 16 h. After cooling to ambient temperature, the reaction mixture was dry loaded onto silica gel and purified by flash column chromatography (*n*-hexane/EtOAc = 7:1) to yield the product **133ia** (92 mg, 66%) as a white solid.

H/D Exchange Experiments

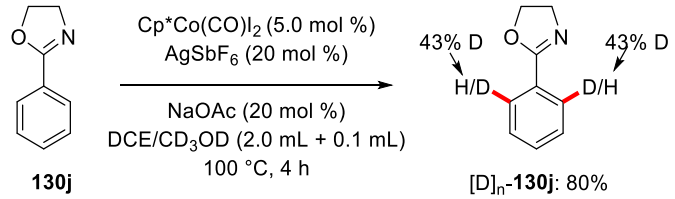
Cobalt-Catalyzed H/D Exchange in Substrate 130i with CD_3OD as the Co-solvent in the Absence of 132a:



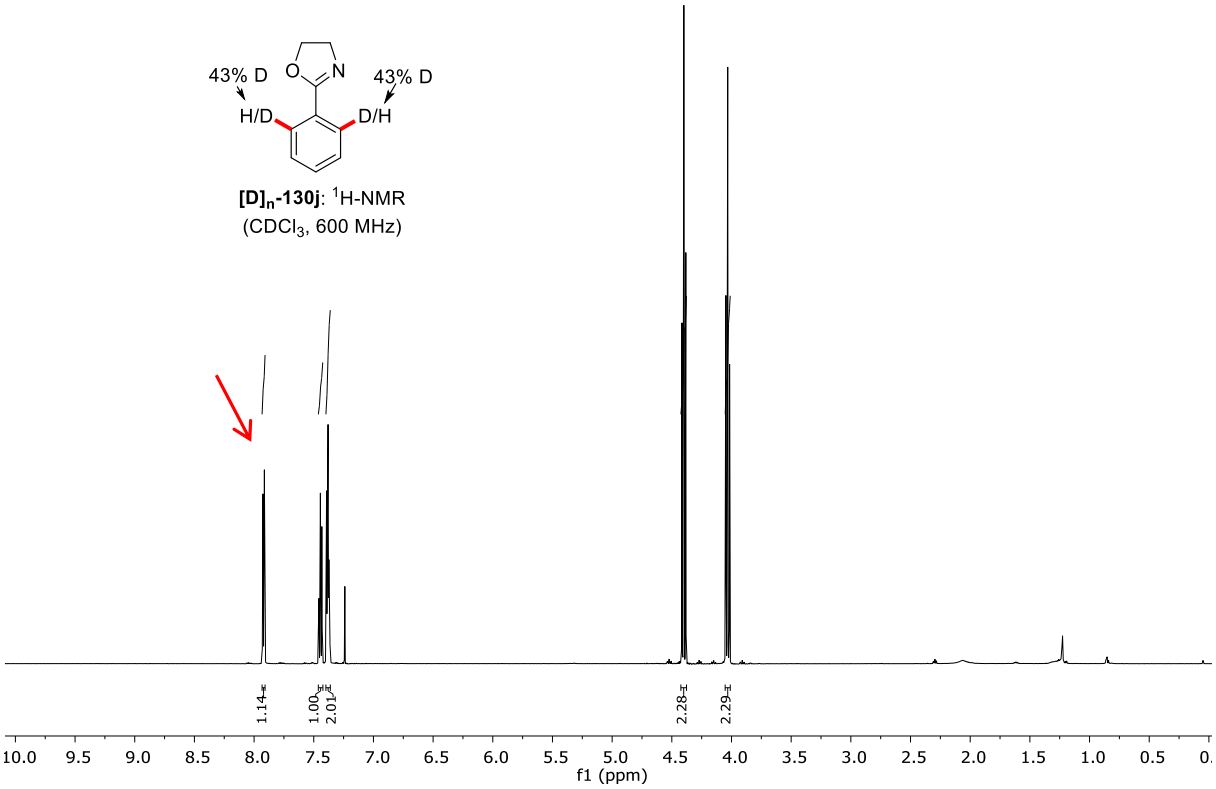
A suspension of oxazoline **130i** (81 mg, 0.50 mmol), [Cp*Co(CO)I_2] (11.9 mg, 5.0 mol %), $AgSbF_6$ (34 mg, 20 mol %) and NaOAc (8.2 mg, 10 mol %) in a solvent mixture of DCE (2.0 mL) and CD_3OD (0.10 mL) was stirred at 100 °C for 16 h under argon atmosphere. After cooling to ambient temperature, the reaction mixture was evaporated *in vacuo* and the remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to yield $[D]_n$-**130i** (55 mg, 68%) as a pale yellow solid. The D-incorporation in $[D]_n$-**130i** was estimated by ^{1}H-NMR spectroscopy.



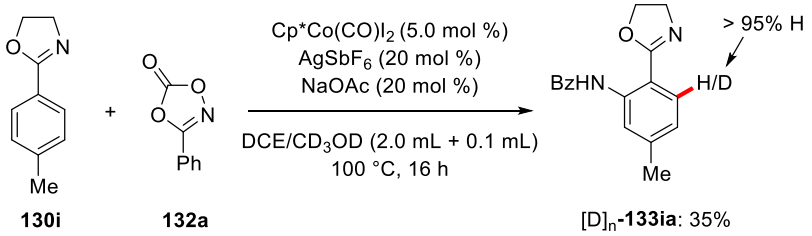
Cobalt-Catalyzed H/D Exchange in Substrate 130j with CD_3OD as the Co-solvent in the absence of 132a:



A suspension of 2-phenyl-4,5-dihydrooxazole **(130j)** (74 mg, 0.50 mmol), [Cp*Co(CO)I_2] (11.9 mg, 5.0 mol %), $AgSbF_6$ (34 mg, 20 mol %) and NaOAc (8.2 mg, 20 mol %) in a solvent mixture of DCE (2.0 mL) and CD_3OD (0.10 mL) was stirred at 100 °C for 4 h under argon atmosphere. After cooling to ambient temperature, the reaction mixture was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to yield $[D]_n$-**130j** (59 mg, 80%) as a pale yellow oil. The D-incorporation in $[D]_n$-**130j** was estimated by ^{1}H-NMR spectroscopy.

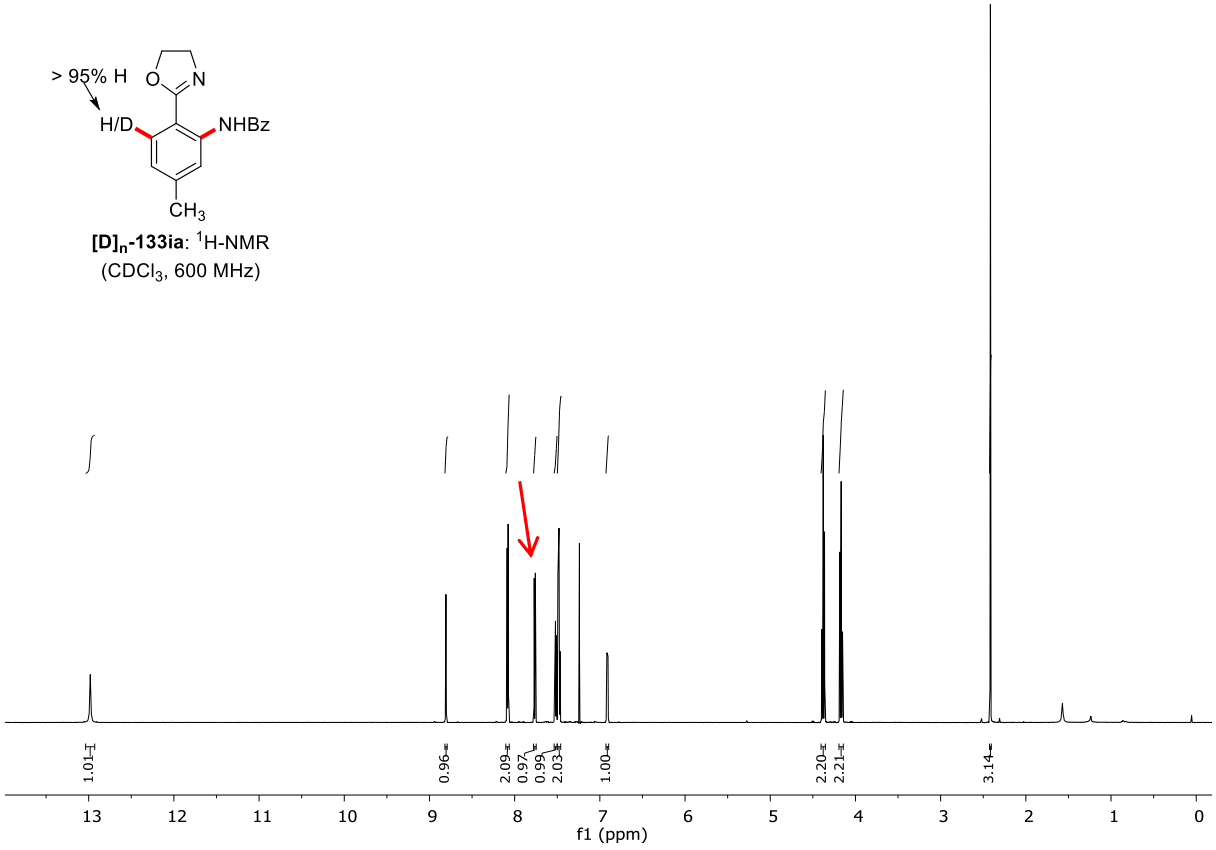


Cobalt-Catalyzed H/D Exchange in Substrate 130i with CD_3OD as the Co-solvent in the Presence of 132a:



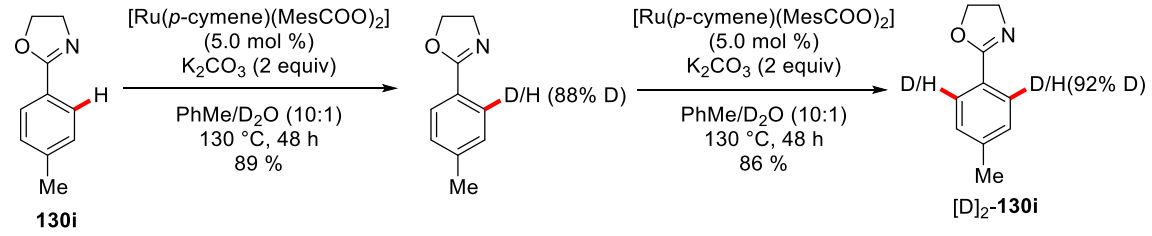
130i **132a** [D]$_n$-**133ia**: 35%

A suspension of oxazoline **130i** (81 mg, 0.50 mmol), **132a** (98 mg, 0.60 mmol), [Cp*Co(CO)I_2] (11.9 mg, 5.0 mol %), $AgSbF_6$ (34 mg, 20 mol %) and NaOAc (8.2 mg, 20 mol %) in a solvent mixture of DCE (2.0 mL) and CD_3OD (0.10 mL) was stirred at 100 °C for 16 h under argon atmosphere. After cooling to ambient temperature, the reaction mixture was evaporated *in vacuo* and the remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc) and then by GPC to yield [D]$_n$-**133ia** (49 mg, 35%) as a white solid. The D-incorporation in [D]$_n$-**133ia** was estimated by ^{1}H-NMR spectroscopy.

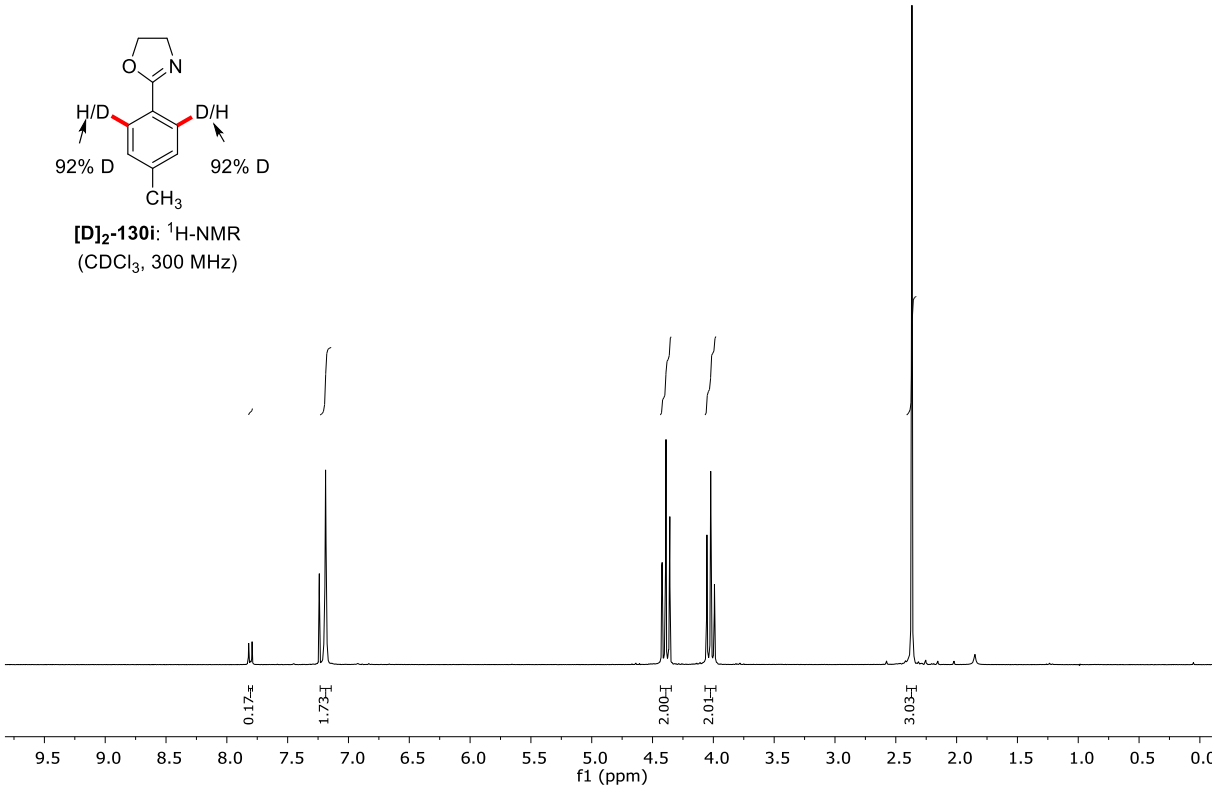


Kinetic Isotope Effects Experiments

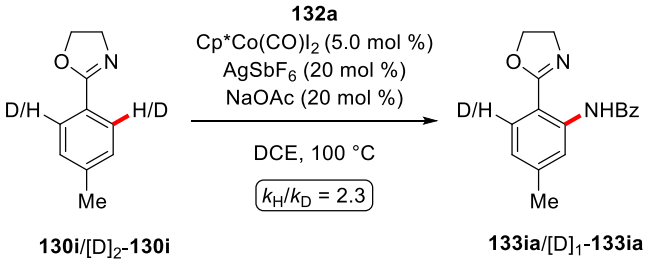
Synthesis of Deuterated Substrate [D]$_2$-130i



To a 25 mL Schlenk flask was added **130i** (967 mg, 6.0 mmol), [Ru(*p*-cymene)(MesCO$_2$)$_2$] (168 mg, 5.0 mol %), K_2CO_3 (1.66 g, 12.0 mmol), D_2O (0.80 mL), and PhMe (8.0 mL) under argon atmosphere. The mixture was stirred at 130 °C for 48 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc, dried with K_2CO_3 and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (*n*-hexane/EtOAc 2:1) to give the deuterated product as a pale yellow solid (871 mg, 89%). ^{1}H-NMR analysis showed 88% Deuterium incorporation in the *ortho*-positions. The same procedure was repeated again: The substrate (871 mg, 5.34 mmol) was dissolved in PhMe (6.0 mL), [Ru(*p*-cymene)(MesCO$_2$)$_2$] (149 mg, 5.0 mol %), K_2CO_3 (1.48 g, 10.7 mmol) and D_2O (0.60 mL) was added. This mixture was stirred at 130 °C for 48 h. Following the same work-up procedure as above, the deuterated product [D]$_2$-**130i** was isolated as a pale yellow solid (748 mg, 86%). ^{1}H-NMR analysis showed 92% Deuterium incorporation in the *ortho*-positions.



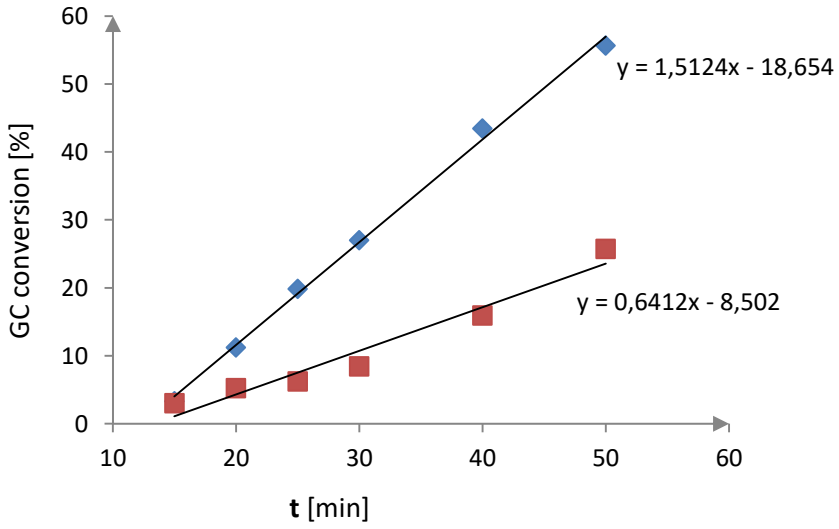
Parallel Experiments



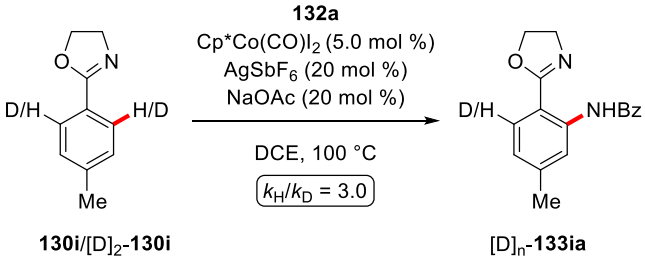
130i/[D]$_2$-**130i** **133ia**/[D]$_1$-**133ia**

Two independent reactions with **130i** or deuterated substrate [D]$_2$-**130i** under the standard conditions were performed: Suspensions of dioxazolone **132a** (196 mg, 1.2 mmol), substrate **130i** (161 mg, 1.0 mmol) or [D]$_2$-**130i** (163 mg, 1.0 mmol), [Cp*Co(CO)I$_2$] (23.0 mg, 5.0 mol %), $AgSbF_6$ (68.7 mg, 20 mol %), NaOAc (16.4 mg, 20 mol %) and internal standard *n*-dodecane (101 mg, 0.60 mmol) in DCE (4.0 mL) were stirred at 100 °C for 15 min, 20 min, 25 min, 30 min, 40 min, 50 min under an atmosphere of argon, respectively. The conversion to the products **133ia** or [D]$_1$-**133ia** was monitored by GC analysis.

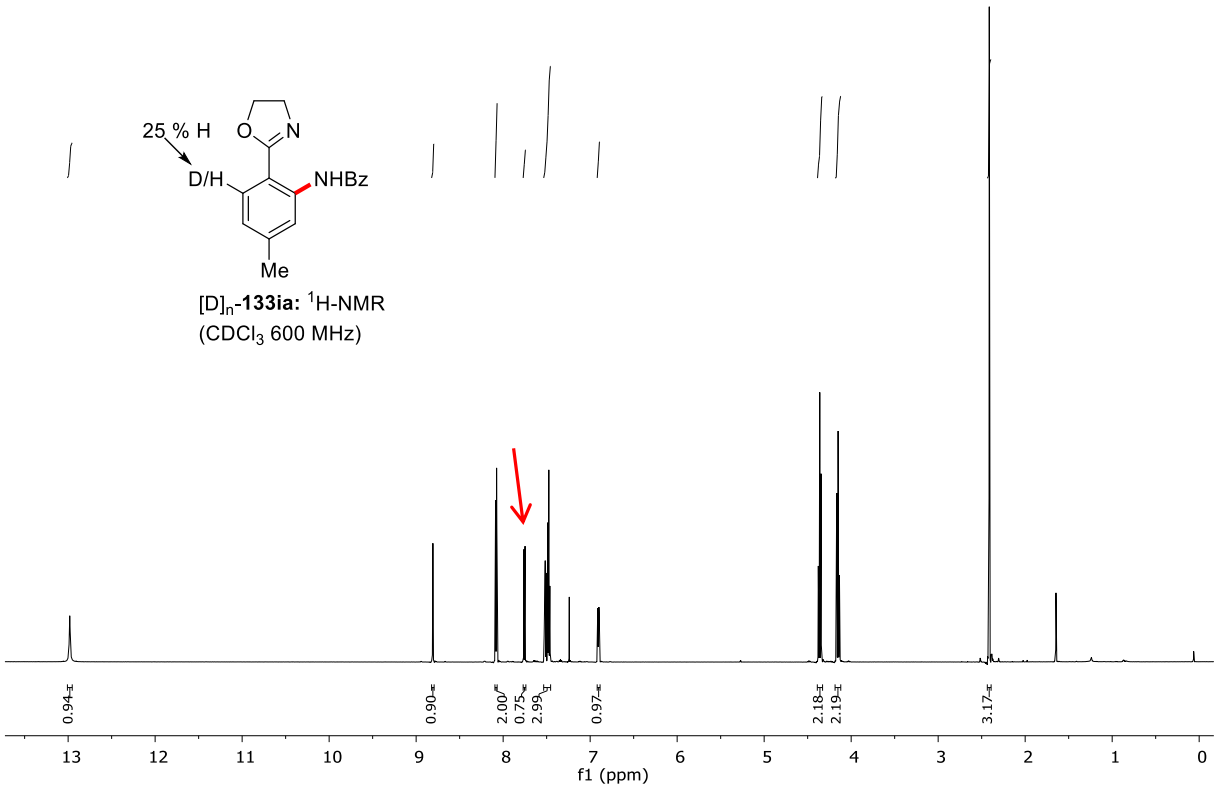
t [min]	15	20	25	30	40	50
3aa [%]	3.3	11.2	19.8	27.0	43.4	55.6
[D]$_1$-3aa [%]	3.0	5.2	6.2	8.4	15.9	25.7



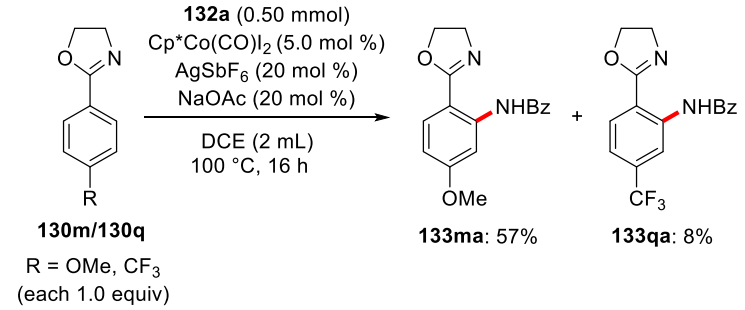
Competition Experiment



130i (81 mg, 0.50 mmol) and [D]$_2$-**130i** (82 mg, 0.50 mmol) were added to one test tube with stirring bar, followed by dioxazolone **132a** (82 mg, 0.50 mmol), [Cp*Co(CO)I$_2$] (12 mg, 5.0 mol %), AgSbF$_6$ (34 mg, 20 mol %), NaOAc (16.4 mg, 20 mol %) and DCE (2.0 mL), and the mixture was stirred at 100 °C for 16 h under argon. After cooling to ambient temperature, the volatiles were removed under reduced pressure and the mixture was purified by flash chromatography on silica gel to afford the amidation product [D]$_n$-**133ia** (36 mg, 26%) as a white solid. The KIE value of the competition experiment was estimated to be 3.0 by ^{1}H NMR analysis.

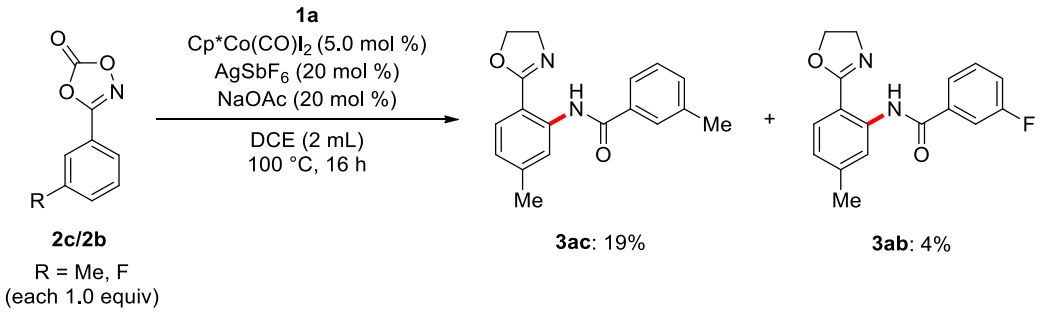


Intermolecular Competition Experiment between oxazolines 130q and 130m



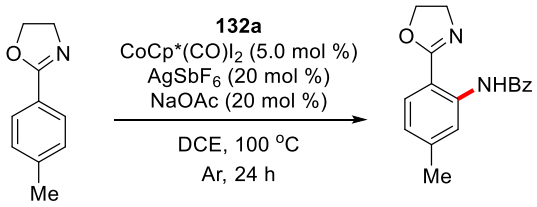
A suspension of 3-phenyl-1,4,2-dioxazol-5-one (**132a**) (81 mg, 0.50 mmol), oxazoline **130m** (89 mg, 0.50 mmol), oxazoline **130q** (108 mg, 0.50 mmol), [Cp*Co(CO)I_2] (11.9 mg, 5.0 mol %), $AgSbF_6$ (34 mg, 20 mol %) and NaOAc (8.2 mg, 20 mol %) in DCE (2.0 mL) was stirred at 100 °C for 16 h under an atmosphere of argon. At ambient temperature, 1,3,5-trimethoxybenzene (16.8 mg, 0.10 mmol) was added as internal standard, the conversion of **133ma** and **133qa** was calculated based on crude ^{1}H-NMR analysis.

Intermolecular Competition Experiment between amidation reagents 132b and 132c



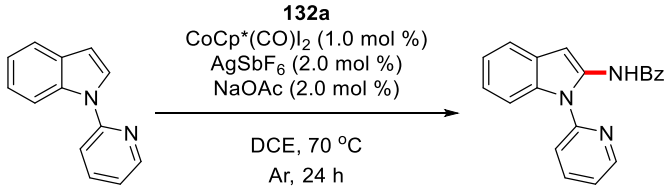
A suspension of oxazoline **130i** (81 mg, 0.50 mmol), amidation reagent **132b** (88 mg, 0.50 mmol), **132c** (82 mg, 0.50 mmol), [Cp*Co(CO)I_2] (11.9 mg, 5.0 mol %), $AgSbF_6$ (34 mg, 20 mol %) and NaOAc (8.2 mg, 20 mol %) in DCE (2.0 mL) was stirred at 100 °C for 16 h under an atmosphere of argon. After cooling to ambient temperature, the reaction mixture was dry loaded onto silica gel and purified by column chromatography (*n*-hexane/EtOAc 6:1) to afford a mixture of **133ib** and **133ic** (34 mg). The ratio of the two products was determined by ^{1}H-NMR analysis.

Procedures for Gram-Scale Reactions



130i **133ia**: 62%

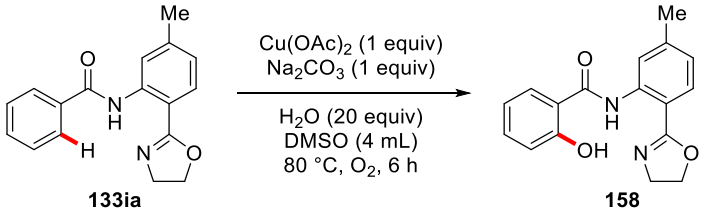
To a 100 mL Schlenk flask was added substrates **130i** (6.0 mmol, 967 mg), **132a** (1.17 g, 7.2 mmol), [Cp*Co(CO)I_2] (138 mg, 5.0 mol %), $AgSbF_6$ (412 mg, 20 mol %), NaOAc (98 mg, 20 mol %) and DCE (24 mL). This mixture was stirred at 100 °C for 24 h under an atmosphere of argon. After cooling to ambient temperature, the reaction mixture was dry loaded onto silica gel and purified by flash column chromatography (*n*-hexane/EtOAc = 6:1) to afford the desired product **133ia** as white solid (1.04 g, 62%).



102b **154ba**: 98%

To a 100 mL Schlenk tube were added substrates **102b** (6.0 mmol, 1.16 g), **132a** (1.17 g, 7.2 mmol), [Cp*Co(CO)I_2] (28 mg, 1.0 mol %), $AgSbF_6$ (41 mg, 2.0 mol %), NaOAc (9.8 mg, 2.0 mol %) and DCE (24 mL). This mixture was stirred at 70 °C for 24 h under an atmosphere of argon. After cooling to ambient temperature, the reaction mixture was dry loaded onto silica gel and purified by flash column chromatography (*n*-hexane/EtOAc 2:1) to afford the desired product **154ba** as white solid (1.84 g, 98%).

Diversification of 2-Amidoaryloxazolines 3

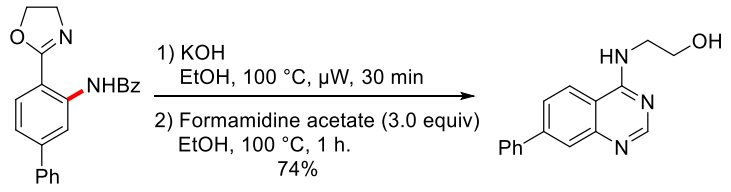


133ia **158**

***N*-[2-(4,5-Dihydrooxazol-2-yl)-5-methylphenyl]-2-hydroxybenzamide (158):** Following a modified procedure,[151] **133ia** (0.20 mmol, 56 mg), H_2O (72 mg, 4.0 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Na_2CO_3 (21 mg, 0.20 mmol), and DMSO (4.0 mL) were added to a 25 mL Schlenk tube. The reaction tube was evacuated and backfilled with O_2 6 times. After stirring at 80 °C for 6 h, the reaction mixture was diluted with EtOAc (20 mL) and washed with NH_4OH (25%, 20 mL) and brine (20 mL). The organic fraction was dried

over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) to give the hydroxylated product **158** as a white solid (53 mg, 89%).

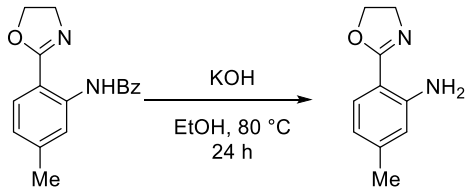
M. p. = 144−145 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 13.17 (s, 1H), 12.44 (s, 1H), 8.62 (s, 1H), 7.89 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.40 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H), 6.99 (dd, *J* = 8.6, 1.2 Hz, 1H), 6.96–6.85 (m, 2H), 4.39 (td, *J* = 9.3, 1.3 Hz, 2H), 4.17 (td, *J* = 9.3, 1.3 Hz, 2H), 2.41 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 169.7 (C_q), 165.0 (C_q), 162.3 (C_q), 143.4 (C_q), 139.1 (C_q), 134.2 (CH), 129.2 (CH), 126.9 (CH), 123.9 (CH), 120.7 (CH), 118.8 (CH), 118.5 (CH), 115.6 (C_q), 111.4 (C_q), 66.3 (CH_2), 54.5 (CH_2), 22.1 (CH_3). **IR** (ATR): 2981, 2908, 1628, 1581, 1313, 1261, 1149, 813, 742, 517 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 296 (50) [M$^+$], 280(10), 203 (25), 176 (100), 160 (20), 145 (20), 121 (20). **HR-MS** (EI) *m/z* calcd for $C_{17}H_{16}N_2O_3$ [M$^+$] 296.1161, found 296.1166.



133oa **159**

2-[(7-Phenylquinazolin-4-yl)amino]ethan-1-ol (159): To a 5 mL sealed tube was added **133oa** (51 mg, 0.15 mmol), KOH (336 mg, 6.0 mmol), EtOH (2.0 mL). The reaction mixture was irradiated with microwave at 100 °C for 30 min under air. Upon completion, the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (4 × 20 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. Following a modified procedure,[12] the residue was then dissolved in EtOH (2.0 mL), and formamidine acetate (47 mg, 3.0 equiv) was added. The reaction mixture was heated at 90 °C for 1 hour. After cooling to ambient temperature, the reaction mixture was dry loaded onto silica gel and purified by column chromatography (DCM/MeOH 10:1) to yield the product **159** (29 mg, 74%) as an off-white solid.

M. p. = 209−210 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 8.48 (s, 1H), 8.34 (d, *J* = 8.6 Hz, 1H), 8.29–8.24 (m, 1H), 7.91 (d, *J* = 1.8 Hz, 1H), 7.85–7.82 (m, 3H), 7.56–7.49 (m, 2H), 7.47–7.40 (m, 1H), 4.79 (s, 1H), 3.76–3.59 (m, 4H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 159.3 (C_q), 155.4 (CH), 149.5 (C_q), 143.8 (C_q), 138.8 (C_q), 129.0 (CH), 128.2 (CH), 127.0 (CH), 124.5 (CH), 124.2 (CH), 123.5 (CH), 114.0 (C_q), 59.2 (CH_2), 43.3 (CH_2). **IR** (ATR): 3337, 3061, 2830, 1584, 1428, 1347, 1064, 755, 512 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 265 (15) [M$^+$], 247 (40), 222 (100), 207 (20), 193 (10), 177 (10). **HR-MS** (EI) *m/z* calcd for $C_{16}H_{15}N_3O$ [M$^+$] 265.1215, found 265.1223.



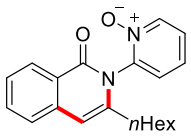
133ia **178**

2-(4, 5-Dihydrooxazol-2-yl)-5-methylaniline (S8)

133ia (140 mg, 0.50 mmol), KOH (1.12 g, 20 mmol), EtOH (10 mL) were added to a 50 mL sealed tube. The reaction mixture was stirred at 80 °C for 24 h under air. After cooling to ambient temperature, the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (4 × 20 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc 5:1) to give **178** as a pale yellow solid (83 mg, 93%).

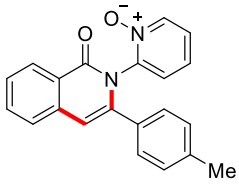
M. p. = 93−94 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.56 (d, *J* = 8.0 Hz, 1H), 6.50–6.45 (m, 2H), 5.96 (br, 2H), 4.28 (td, *J* = 9.3, 1.0 Hz, 2H), 4.06 (td, *J* = 9.3, 1.0 Hz, 2H), 2.25 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 164.8 (C_q), 148.4 (C_q), 142.4 (C_q), 129.5 (CH), 117.4 (CH), 115.9 (CH), 106.8 (C_q), 65.6 (CH_2), 54.9 (CH_2), 21.5 (CH_3). **IR** (ATR): 3426, 3308, 2979, 2876, 1607, 1366, 1247, 1047, 810, 680 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 176 (100) [M^+], 145 (40), 132 (25), 118 (10), 104 (10). **HR-MS** (EI) *m/z* calcd for $C_{17}H_{16}N_2O_3$ [M^+] 176.0950, found 176.0949.

5.3.6 Cobalt-Catalyzed Oxidase C−H/N−H Alkyne Annulation



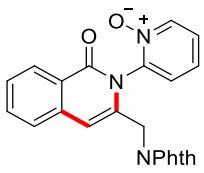
2-[3-*n*-Hexyl-1-oxoisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134ae): The general procedure **G** was followed, using aromatic amide **85a** (107 mg, 0.50 mmol) and alkyne **59e** (66 mg, 0.60 mmol). Purification by column chromatography on silica gel (CH_2Cl_2/acetone 2:1) yielded **134ae** (124 mg, 77%) as a colorless solid.

M. p. = 100–101 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.38–8.24 (m, 2H), 7.64–7.58 (m, 1H), 7.48–7.37 (m, 3H), 7.36–7.31 (m, 2H), 6.41 (s, 1H), 2.40–2.24 (m, 1H), 2.21–2.06 (m, 1H), 1.57–1.46 (m, 2H), 1.29–1.11 (m, 6H), 0.82 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 162.5 (C_q), 144.4 (C_q), 142.5 (C_q), 140.5 (CH), 137.3 (C_q), 133.0 (CH), 128.0 (CH), 127.8 (CH), 126.1 (CH), 125.9 (CH), 125.6 (CH), 125.3 (CH), 124.3 (C_q), 104.8 (CH), 31.8 (CH_2), 31.2 (CH_2), 28.6 (CH_2), 27.4 (CH_2), 22.2 (CH_2), 13.8 (CH_3). **IR** (ATR): 2962, 2856, 1662, 1624, 1591, 1561, 1467, 1308, 994, 820 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 323 (10) [M+H$^+$], 322 (50) [M$^+$], 306 (30), 305 (100), 265 (20), 251 (60), 234 (95). **HR-MS** (EI) *m/z* calcd for $C_{20}H_{22}N_2O_2$ [M$^+$] 322.1681, found 322.1672.



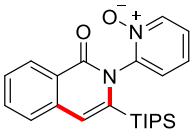
2-[1-Oxo-3-(*p*-tolyl) isoquinolin-2(1*H*)-yl] pyridine 1-oxide (134af): The general procedure **G** was followed, using aromatic amide **85a** (107 mg, 0.50 mmol) and alkyne **59f** (70 mg, 0.60 mmol). Purification by column chromatography on silica gel (CH_2Cl_2/acetone 2:1) yielded **134af** (149 mg, 91%) as a colorless solid.

M. p. = 238–239 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.39–8.36 (m, 1H), 8.19–8.12 (m, 1H), 7.70–7.59 (m, 1H), 7.52–7.36 (m, 2H), 7.31–7.20 (m, 2H), 7.14–7.00 (m, 3H), 7.00–6.94 (m, 2H), 6.53 (s, 1H), 2.22 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 161.8 (C_q), 145.5 (C_q), 142.6 (C_q), 139.8 (CH), 138.9 (C_q), 137.0 (C_q), 133.2 (CH), 131.9 (C_q), 128.8 (CH), 128.2 (CH), 127.6 (CH), 127.5 (CH), 126.8 (CH), 126.1 (CH), 125.3 (CH), 125.0 (CH), 124.7 (C_q), 107.8 (CH), 21.1 (CH_3). **IR** (ATR): 3062, 1657, 1621, 1600, 1480, 1422, 1260, 1141, 890, 758 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 329 (5) [M+H$^+$], 328 (10) [M$^+$], 312 (30), 283 (30), 208 (25), 195 (100), 165 (50). **HR-MS** (EI) *m/z* calcd for $C_{21}H_{16}N_2O_2$ [M$^+$] 328.1212, found 328.1213.



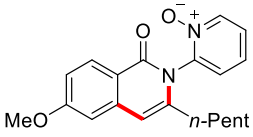
2-[3-{(1,3-Dioxoisoindolin-2-yl)methyl}-1-oxoisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134ag): The general procedure **G** was followed, using aromatic amide **85a** (107 mg, 0.50 mmol) and alkyne **59g** (111 mg, 0.60 mmol). The crude product was directly purified by column chromatography on silica gel (*n*-hexane/EtOAc 2:1 → CH_2Cl_2/acetone 1:1) without aqueous work up yielding **134ag** (187 mg, 94%) as a colorless solid.

M. p. = 232–233 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.37–8.28 (m, 2H), 7.83–7.76 (m, 2H), 7.75–7.68 (m, 2H), 7.66 (ddd, *J* = 7.9, 7.2, 1.4 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.49–7.43 (m, 2H), 7.40 (ddd, *J* = 7.7, 6.4, 2.4 Hz, 1H), 7.35 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.75 (s, 1H), 4.75 (dd, *J* = 15.7, 1.0 Hz, 1H), 4.46 (d, J = 15.7 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 167.1 (C_q), 162.3 (C_q), 143.3 (C_q), 140.9 (CH), 136.5 (C_q), 136.0 (C_q), 134.3 (CH), 133.4 (CH), 131.7 (C_q), 128.5 (CH), 128.3 (CH), 127.4 (CH), 126.4 (CH), 126.3 (CH), 125.8 (CH), 125.2 (C_q), 123.4 (CH), 108.6 (CH), 38.9 (CH_2). **IR** (ATR): 3513, 2283, 3062, 1717, 1668, 1635, 1603, 1420, 1386, 1115, 725 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 398 (2) [M+H$^+$], 380 (15), 303 (10), 264 (10), 234 (100), 205 (20), 160 (40). **HR-MS** (EI) *m/z* calcd for $C_{23}H_{15}N_3O_4$ [M$^+$] 397.1063, found 397.1076.



2-[1-Oxo-3-(triisopropylsilyl)isoquinolin-2(1*H*)-yl] pyridine 1-oxide (134ah): The general procedure **G** was followed, using aromatic amide **85a** (107 mg, 0.50 mmol) and alkyne **59h** (109 mg, 0.60 mmol). Purification by column chromatography on silica gel (CH_2Cl_2/acetone 2:1) yielded **134ah** (164 mg, 83%) as a colorless solid.

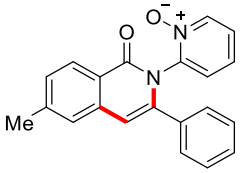
M. p. = 175–177 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.38–8.35 (m, 1H), 8.27 (dd, *J* = 6.4, 1.5 Hz, 1H), 7.71–7.63 (m, 1H), 7.54–7.42 (m, 3H), 7.37–7.27 (m, 2H), 6.83 (s, 1H), 1.10–1.03 (m, 18H), 0.97–0.83 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 163.1 (C_q), 147.2 (C_q), 141.6 (C_q), 140.3 (CH), 136.3 (C_q), 132.9 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 126.1 (CH), 126.0 (CH), 125.8 (C_q), 124.3 (CH), 118.7 (CH), 19.1 (CH_3), 18.6 (CH_3), 12.3 (CH). **IR** (ATR): 2942, 2866, 1650, 1488, 1427, 1334, 1261, 950, 882, 747 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 395 (30) [M+H$^+$], 394 (100) [M$^+$], 386 (10), 385 (40), 379 (25), 377 (60), 369 (60). **HR-MS** (ESI) *m/z* calcd for $C_{23}H_{31}N_2O_2Si$ [M+H$^+$] 395.2149, found 395.2148.



2-[6-Methoxy-1-oxo-3-*n*-pentylisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134bi): The general procedure **G** was followed, using aromatic amide **85b** (122 mg, 0.50 mmol) and alkyne **59i** (58 mg, 0.60 mmol).

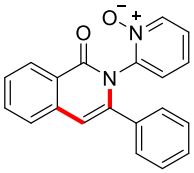
Purification by column chromatography on silica gel (CH_2Cl_2/acetone 1:1) yielded **134bi** (147 mg, 88%) as a colorless solid.

M. p. = 202–203 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.34–8.28 (m, 1H), 8.19 (d, J = 8.8 Hz, 1H), 7.42–7.37 (m, 1H), 7.33–7.26 (m, 2H), 6.92 (dd, J = 8.9, 2.5 Hz, 1H), 6.80 (d, J = 2.5 Hz, 1H), 6.32 (s, 1H), 3.83 (s, 3H), 2.31–2.19 (m, 1H), 2.15–2.01 (m, 1H), 1.55–1.40 (m, 2H), 1.23–1.10 (m, 4H), 0.78 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 163.3 (C_q), 162.0 (C_q), 144.3 (C_q), 143.1 (C_q), 140.3 (CH), 139.5 (C_q), 129.9 (CH), 127.9 (CH), 125.8 (CH), 125.3 (CH), 117.9 (C_q), 115.4 (CH), 106.6 (CH), 104.6 (CH), 55.3 (CH_3), 31.7 (CH_2), 31.0 (CH_2), 27.0 (CH_2), 22.0 (CH_2), 13.7 (CH_3). **IR** (ATR): 3049, 2926, 2866, 1697, 1665, 1632, 1598, 1485, 1252, 866 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 395 (2) [M+H$^+$], 394 (5) [M$^+$], 378 (60), 359 (20), 249 (100), 235 (60), 206 (20). **HR-MS** (EI) *m/z* calcd for $C_{20}H_{22}N_2O_3$ [M$^+$], 338.1630, found 338.1632.



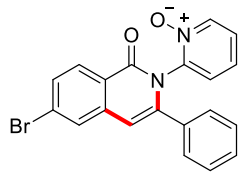
2-[6-Methyl-1-oxo-3-phenylisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134cj): The general procedure **G** was followed, using aromatic amide **85a** (114 mg, 0.50 mmol) and alkyne **59j** (61 mg, 0.60 mmol). Purification by column chromatography on silica gel (CH_2Cl_2/acetone 2:1) yielded **134cj** (158 mg, 96%) as a colorless solid.

M. p. = 224–225 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.26 (d, J = 8.0 Hz, 1H), 8.16–8.13 (m, 1H), 7.37–7.33 (m, 2H), 7.27–7.24 (m, 2H), 7.21–7.13 (m, 3H), 7.10–7.05 (m, 2H), 7.02–6.96 (m, 1H), 6.48 (s, 1H), 2.44 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 161.7 (C_q), 145.4 (C_q), 143.9 (C_q), 142.5 (C_q), 139.8 (CH), 137.0 (C_q), 134.8 (C_q), 128.8 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.6 (CH), 126.0 (CH), 125.3 (CH), 124.9 (CH), 122.5 (C_q), 107.8 (CH), 21.7 (CH_3). **IR** (ATR): 3055, 1658, 1627, 1607, 1482, 1433, 1369, 1262, 773, 694 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 329 (5) [M+H$^+$], 328 (20) [M$^+$], 311 (10), 283 (15), 208 (20), 181 (100), 165 (30). **HR-MS** (EI) *m/z* calcd for $C_{21}H_{16}N_2O_2$ [M$^+$] 328.1212, found 328.1215.

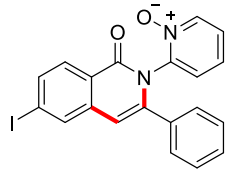


2-[1-Oxo-3-phenylisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134aj): The general procedure **G** was followed, using aromatic amide **85a** (107 mg, 0.50 mmol) and alkyne **59j** (61 mg, 0.60 mmol). Purification by column chromatography on silica gel (CH_2Cl_2/acetone 2:1) yielded **134aj** (149 mg, 95%) as a colorless solid.

M. p. = 226–227 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.41–8.38 (m, 1H), 8.18–8.14 (m, 1H), 7.68–7.64 (m, 1H), 7.52 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.48–7.44 (m, 1H), 7.41–7.36 (m, 2H), 7.25–7.17 (m, 3H), 7.12–7.09 (m, 2H), 7.04–7.00 (m, 1H), 6.57 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 161.8 (C_q), 145.4 (C_q), 142.5 (C_q), 139.9 (CH), 136.9 (C_q), 134.7 (C_q), 133.2 (CH), 128.9 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 127.5 (CH), 126.9 (CH), 126.2 (CH), 125.3 (CH), 125.0 (CH), 124.8 (C_q), 107.9 (CH). **IR** (ATR): 3073, 1658, 1622, 1602, 1482, 1425, 1256, 1142, 889, 760 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 315 (5) [M+H$^+$], 314 (20) [M$^+$], 298 (20), 269 (30), 194 (30), 181 (100), 165 (30). **HR-MS** (EI) *m/z* calcd for $C_2H_{14}N_2O_2$ [M$^+$] 314.1055, found 314.1044.

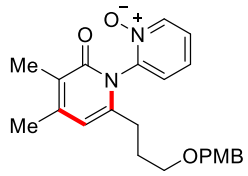


2-[6-Bromo-1-oxo-3-phenylisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134dj): The general procedure **G** was followed, using aromatic amide **85d** (146 mg, 0.50 mmol), alkyne **59j** (61 mg, 0.60 mmol). Purification by column chromatography on silica gel (CH_2Cl_2/acetone 2:1) yielded **134dj** (187 mg, 95%) as a colorless solid.
M. p. = 210–212 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.25 (d, *J* = 8.6 Hz, 1H), 8.21–8.17 (m, 1H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.57 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.40–7.35 (m, 2H), 7.25–7.17 (m, 3H), 7.17–7.09 (m, 2H), 7.08–7.02 (m, 1H), 6.49 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 161.5 (C_q), 145.2 (C_q), 144.1 (C_q), 140.0 (CH), 138.5 (C_q), 134.5 (C_q), 130.4 (CH), 130.2 (CH), 129.3 (CH), 128.7 (CH), 128.6 (C_q), 128.3 (CH), 127.9 (CH), 127.6 (CH), 125.6 (CH), 125.0 (CH), 123.6 (C_q), 106.8 (CH). **IR** (ATR): 3055, 1666, 1628, 1589, 1490, 1470, 1366, 1255, 763, 681 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 394 (15) [M$^+$] (^{81}Br), 392 (15) [M$^+$] (^{79}Br), 376 (25), 349 (25) (^{81}Br), 347 (25) (^{81}Br), 272 (10), 268 (20), 181 (100), 165 (30). **HR-MS** (EI) *m/z* calcd for $C_{20}H_{13}{}^{79}BrN_2O_2$ [M$^+$] 392.0160, found 392.0164.



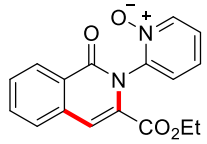
2-[6-Iodo-1-oxo-3-phenylisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134ej): The general procedure **G** was followed, using aromatic amide **85e** (170 mg, 0.50 mmol) and alkyne **59j** (61 mg, 0.60 mmol). Purification by column chromatography on silica gel (CH_2Cl_2/acetone 2:1) yielded **134ej** (200 mg, 91%) as a colorless solid.
M. p. = 249–250 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.19 (d, *J* = 6.5 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 1.6 Hz, 1H), 7.77 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.39–7.33 (m, 2H), 7.25–7.17 (m, 3H), 7.17–7.08 (m, 2H),

7.07–7.02 (m, 1H), 6.46 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 161.7 (C_q), 145.2 (C_q), 143.9 (C_q), 140.1 (CH), 138.4 (C_q), 136.0 (CH), 135.1 (CH), 134.5 (C_q), 129.8 (CH), 129.3 (CH), 128.3 (CH), 127.9 (CH), 127.6 (CH), 125.6 (CH), 125.1 (CH), 124.1 (C_q), 106.6 (CH), 101.4 (C_q). **IR** (ATR): 3055, 1666, 1626, 1599, 1583, 1490, 1428, 1365, 892 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 440 (20) [M^+], 424 (15), 395 (15), 320 (20), 208 (20), 296 (10), 268 (10), 181 (100). **HR-MS** (EI) *m/z* calcd for $C_{20}H_{13}IN_2O_2$ [M^+] 440.0022, found 442.0010.



6-[3-{(4-Methoxybenzyl) oxy} propyl]-3, 4-dimethyl-2-oxo-2*H*-[1, 2'-bipyridine] 1'-oxide (134fk): The general procedure **G** was followed, using aromatic amide **85f** (147 mg, 0.50 mmol), alkyne **59k** (127 mg, 0.60 mmol) and $Co(OAc)_2$ (18 mg, 20 mol %). Purification by column chromatography on silica gel (CH_2Cl_2/acetone 2:1) yielded **134fk** (106 mg, 54%) as a colorless solid.

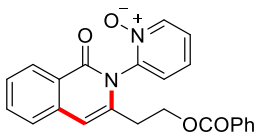
M. p. = 105–106 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.29 (dd, *J* = 4.7, 3.1 Hz, 1H), 7.37–7.22 (m, 3H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.92 (s, 1H), 4.28 (s, 2H), 3.77 (s, 3H), 3.42–3.20 (m, 2H), 2.37–2.16 (m, 2H), 2.13 (s, 3H), 2.02 (s, 3H), 1.71 (tt, *J* = 6.8, 6.8 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 162.7 (C_q), 159.1 (C_q), 147.5 (C_q), 144.5 (C_q), 143.8 (C_q), 140.5 (CH), 130.2 (C_q), 129.1 (CH), 127.5 (CH), 125.8 (CH), 125.4 (CH), 123.8 (C_q), 113.6 (CH), 108.8 (CH), 72.3 (CH_2), 68.3 (CH_2), 55.2 (CH_3), 28.4 (CH_2), 27.6 (CH_2), 20.0 (CH_3), 12.2 (CH_3). **IR** (ATR): 3051, 2918, 2849, 1652, 1593, 1510, 1243, 1098, 1030, 763 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 394 (5) [M^+], 377 (10), 273 (15), 241 (40), 229 (60), 213 (30), 121 (100). **HR-MS** (ESI) *m/z* calcd for $C_{23}H_{27}N_2O_4$ [M+H^+] 395.1965, found 395.1958.



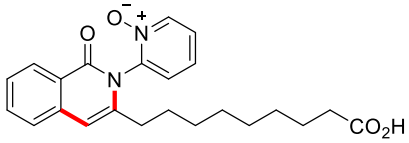
2-[3-(Ethoxycarbonyl)-1-oxoisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134al): The general procedure **G** was followed, using amide **85a** (107 mg, 0.50 mmol) and alkyne **59l** (59 mg, 0.60 mmol). Purification by column chromatography on silica gel (CH_2Cl_2/acetone 2:1) yielded **134al** (138 mg, 89%) as a colorless solid.

M. p. = 172–173 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.39 (dd, *J* = 8.0, 0.7 Hz, 1H), 8.24 (d, *J* = 6.3 Hz, 1H), 7.76–7.69 (m, 1H), 7.67–7.62 (m, 1H), 7.60–7.55 (m, 2H), 7.46 (s, 1H), 7.43–7.35 (m, 1H), 7.36–7.27 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 161.5 (C_q), 161.3 (C_q), 144.3 (C_q), 139.7 (CH), 134.8 (C_q), 133.6 (CH), 131.3 (C_q), 129.2 (CH), 128.6 (CH), 127.8 (CH), 127.4 (C_q), 127.0 (CH), 125.6 (CH), 124.8 (CH), 112.7 (CH), 61.9 (CH_2), 13.8 (CH_3). **IR** (ATR): 3113, 2991, 2903,

1718, 1665, 1479, 1432, 1248, 785, 690 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 311 (10) [M+H^+], 310 (30) [M^+], 294 (10), 249 (30), 237 (100), 209 (80), 195 (20). **HR-MS** (EI) *m/z* calcd for $C_{17}H_{14}N_2O_4$ [M^+] 310.0954, found 310.0963.



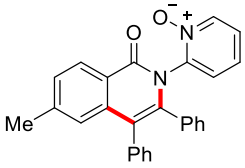
2-[3-(2-(Benzoyloxy)ethyl)-1-oxoisoquinolin-2(1*H*)-yl]pyridine 1-oxide (134am): The general procedure **G** was followed, using amide **85a** (107 mg, 0.50 mmol) and alkyne **59m** (104 mg, 0.60 mmol). Purification by column chromatography on silica gel (CH_2Cl_2/acetone 2:1) yielded **134am** (178 mg, 92%) as a colorless solid.
M. p. = 143–144 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.44–8.40 (m, 1H), 8.38–8.32 (m, 1H), 8.00–7.93 (m, 2H), 7.69–7.63 (m, 1H), 7.59–7.51 (m, 2H), 7.50–7.37 (m, 6H), 6.56 (s, 1H), 4.58–4.42 (m, 2H), 2.90 (dt, *J* = 16.0, 6.9 Hz, 1H), 2.68 (dt, *J* = 16.0, 6.9 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.2 (C_q), 162.6 (C_q), 144.0 (C_q), 140.8 (CH), 138.2 (C_q), 137.0 (C_q), 133.4 (CH), 133.2 (CH), 129.7 (C_q), 129.6 (CH), 128.4 (CH), 128.2 (CH), 128.2 (CH), 126.8 (CH), 126.3 (CH), 125.9 (CH), 125.7 (CH), 124.8 (C_q), 106.4 (CH), 61.9 (CH_2), 31.5 (CH_2). **IR** (ATR): 3061, 1718, 1671, 1632, 1598, 1492, 1245, 1098, 860, 710 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 370 (5), 264 (60), 247 (100), 234 (70), 219 (10), 205 (10), 171 (30), 131 (70). **HR-MS** (ESI) *m/z* calcd for $C_{23}H_{18}N_2O_4K$ [M+K^+], 425.0898, found 425.0896.



2-[3-(8-Carboxyoctyl)-1-oxoisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134an): The general procedure **G** was followed, using amide **85a** (107 mg, 0.50 mmol) and alkyne **59n** (109 mg, 0.60 mmol). The crude product was directly purified by column chromatography on silica gel (*n*-hexane/EtOAc 2:1 → CH_2Cl_2/MeOH 10:1) without aqueous work up yielding **134an** (172 mg, 87%) as a colorless solid.
M. p. = 191–192 ºC. **^{1}H NMR** (300 MHz, DMSO-d_6) δ = 11.90 (s_{br}, 1H), 8.48 (dd, *J* = 6.4, 1.5 Hz, 1H), 8.16–8.10 (m, 1H), 7.80 (dd, *J* = 7.8, 2.4 Hz, 1H), 7.74 (dd, *J* = 7.0, 1.3 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.61–7.45 (m, 3H), 6.61 (s, 1H), 2.32–2.03 (m, 4H), 1.55–1.36 (m, 4H), 1.27–1.06 (m, 8H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ = 174.3 (C_q), 161.5 (C_q), 143.3 (C_q), 142.9 (C_q), 139.9 (CH), 137.2 (C_q), 133.3 (CH), 128.3 (CH), 127.0 (CH), 126.7 (CH), 126.2 (CH), 125.9 (CH), 125.5 (CH), 123.8 (C_q), 104.0 (CH), 33.6 (CH_2), 31.4 (CH_2), 28.4 (CH_2), 28.3 (CH_2), 28.3 (CH_2), 28.2 (CH_2), 26.9 (CH_2), 24.3 (CH_2). **IR** (ATR): 3061, 2926, 2851, 1697, 1671, 1632, 1495, 1436, 1231, 775, cm^{-1}. **MS** (EI) *m/z* (relative intensity) 395 (2) [M+H^+], 394 (5) [M^+], 378 (60), 359 (20), 249 (100), 235 (60), 206 (20). **HR-MS** (EI) *m/z* calcd for $C_{23}H_{26}N_2O_4$ [M^+], 394.1893, found 394.1883.

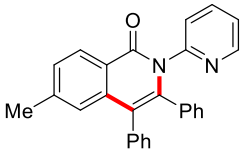
The general procedure **G** was followed, using amide **85c** (107 mg, 0.50 mmol) and alkyne **59d** (107 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1 → CH_2Cl_2/acetone 1:1) yielded **134cd** (149 mg, 74%) and **134cd'** (37 mg, 19%) as colorless solids.

The general procedure **H** was followed, using amide **85c** (107 mg, 0.50 mmol) and alkyne **59d** (107 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) **134cd'** (142 mg, 73%) was obtained as colorless solid.



2-[6-Methyl-1-oxo-3, 4-diphenylisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134cd):

M. p. = 247–248 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.40 (d, *J* = 8.1 Hz, 1H), 8.10 (dd, *J* = 6.5, 1.4 Hz, 1H), 7.44–7.39 (m, 1H), 7.30 (ddd, *J* = 8.1, 1.7, 0.6 Hz, 1H), 7.25–7.22 (m, 2H), 7.16–7.09 (m, 3H), 7.06–7.03 (m, 1H), 7.02–6.97 (m, 2H), 6.97–6.92 (m, 3H), 6.92–6.87 (m, 2H), 2.33 (s, 3H). **^{13}C NMR** (100 MHz, CDCl3) δ = 161.3 (C_q), 145.6 (C_q), 143.8 (C_q), 139.7 (CH), 139.7 (C_q), 138.0 (C_q), 135.7 (C_q), 133.6 (C_q), 131.5 (CH), 131.3 (CH), 130.1 (CH), 128.4 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.0 (CH), 126.9 (CH), 125.5 (CH), 125.1 (CH), 124.7 (CH), 122.8 (C_q), 119.2 (C_q), 22.0 (CH_3). **IR** (ATR): 3056, 1657, 1606, 1481, 1431, 1340, 1323, 760, 711 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 405 (5) [M+H$^+$], 404 (10) [M$^+$], 388 (15), 299 (20), 284 (50), 241 (10), 181 (100). **HR-MS** (EI) *m/z* calcd for $C_{27}H_{20}N_2O_2$ [M$^+$] 404.1525, found 404.1510.

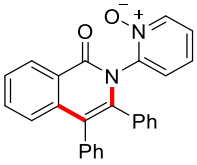


6-Methyl-3, 4-diphenyl-2-(pyridin-2-yl) isoquinolin-1(2*H*)-one (134cd'):

M. p. = 230–232 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.43 (d, *J* = 8.1 Hz, 1H), 8.35 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.55 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.32 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.19 (m, 3H), 7.17–7.08 (m, 3H), 7.08–7.00 (m, 2H), 6.97–6.82 (m, 5H), 2.34 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 162.5 (C_q), 152.7 (C_q), 148.9 (CH), 143.2 (C_q), 140.0 (C_q), 137.8 (C_q), 137.4 (CH), 136.1 (C_q), 134.4 (C_q), 131.6 (CH), 131.6 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 127.1 (CH), 126.9 (CH), 126.7 (CH), 125.3 (CH), 124.9 (CH), 123.3 (C_q), 122.7 (CH), 118.7 (C_q), 22.0 (CH_3). **IR** (ATR): 3059, 1651, 1616, 1589, 1470, 1432, 1324, 758, 698, 585 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 389 (30) [M+H$^+$], 388 (100) [M$^+$], 387 (35) [M–H$^+$], 359 (20), 283 (15), 178 (10), 78 (35). **HR-MS** (EI) *m/z* calcd for $C_{27}H_{20}N_2O$ [M$^+$] 388.1576, found 388.1585.

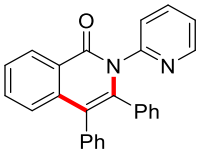
The general procedure **G** was followed, using amide **85a** (107 mg, 0.50 mmol) and alkyne **59d** (109 mg, 0.60 mmol), Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1 → CH_2Cl_2/acetone 1:1) yielded **134ad** (135 mg, 69%) and **134ad'** (49 mg, 26%) as colorless solids.

The general procedure **H** was followed, using amide **85a** (107 mg, 0.50 mmol), alkyne **59d** (109 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 1:1) yielded **134ad'** (157 mg, 84%) as colorless solid.



2-[1-Oxo-3, 4-Diphenylisoquinolin-2(1*H*)-yl) pyridine 1-oxide] (134ad):

M. p. = 264–265 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.52 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.12 (dd, *J* = 6.3, 1.5 Hz, 1H), 7.57 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.49 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.47–7.40 (m, 1H), 7.27–7.20 (m, 3H), 7.16–7.11 (m, 3H), 7.07–7.01 (m, 2H), 7.01–6.87 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 161.5 (C_q), 145.6 (C_q), 139.8 (CH), 139.6 (C_q), 138.0 (C_q), 135.6 (C_q), 133.5 (C_q), 133.1 (CH), 131.5 (CH), 131.3 (CH), 130.1 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.1 (CH), 127.0 (CH), 127.0 (CH), 125.7 (CH), 125.2 (CH), 125.0 (C_q), 124.8 (CH), 119.4 (C_q). **IR** (ATR): 3056, 1666, 1594, 1490, 1431, 1277, 699. cm^{-1}. **MS** (EI) *m/z* (relative intensity) 391 (10) [M+H$^+$], 374 (70), 345 (30), 285 (30), 270 (60), 181 (100). **HR-MS** (ESI) *m/z* calcd for $C_{26}H_{19}N_2O_2$ [M+H$^+$] 391.1441, found 391.1439.

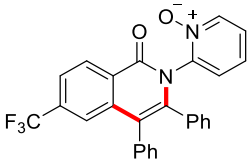


3,4-Diphenyl-2-(pyridin-2-yl) isoquinolin-1(2*H*)-one (134ad'):

M. p. = 251–252 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.55 (dd, *J* = 8.1, 1.4 Hz, 1H), 8.37–8.32 (m, 1H), 7.57–7.52 (m, 2H), 7.48 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.25–7.22 (m, 1H), 7.22–7.16 (m, 3H), 7.16–7.11 (m, 3H), 7.05–6.90 (m, 3H), 6.89–6.84 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 162.4 (C_q), 152.6 (C_q), 148.9 (CH), 139.9 (C_q), 137.6 (C_q), 137.4 (CH), 135.9 (C_q), 134.1 (C_q), 132.5 (CH), 131.4 (CH), 131.4 (CH), 127.9 (CH), 127.8 (CH), 127.1 (CH), 126.9 (CH), 126.7 (CH), 126.7 (CH), 125.5 (CH), 125.4 (C_q), 124.8 (CH), 122.7 (CH), 118.7 (C_q). **IR** (ATR): 3059, 1657, 1589, 1467, 1321, 1156, 996, 777, 590 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 375 (30) [M+H$^+$], 374 (100) [M$^+$], 373 (40) [M–H$^+$], 345 (30), 269 (20), 165 (12), 78 (20). **HR-MS** (EI) *m/z* calcd for $C_{26}H_{18}N_2O$ [M$^+$] 374.1419, found 374.1416.

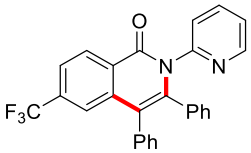
The general procedure **G** was followed, using amide **85g** (141 mg, 0.50 mmol) and alkyne **59d** (107 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1 → CH_2Cl_2/acetone 1:1) yielded **134gd** (104 mg, 44%) and **134gd'** (122 mg, 53%) as colorless solids.

The general procedure **H** was followed, using amide **85g** (141 mg, 0.50 mmol) and alkyne **59d** (107 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **134gd'** (208 mg, 94%) as a colorless solid.



2-[1-Oxo-3, 4-diphenyl-6-(trifluoromethyl)isoquinolin-2(1*H*)-yl] pyridine 1-oxide (134gd):

M. p. = 254–255 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.63 (d, *J* = 8.4 Hz, 1H), 8.15 (dd, *J* = 6.4, 1.5 Hz, 1H), 7.70 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.50 (s, 1H), 7.46–7.37 (m, 1H), 7.32–7.25 (m, 1H), 7.24–7.22 (m, 1H), 7.21–7.17 (m, 2H), 7.16–7.10 (m, 1H), 7.09–7.03 (m, 2H), 7.03–6.87 (m, 5H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 160.6 (C_q), 145.1 (C_q), 141.3 (C_q), 139.8 (CH), 138.2 (C_q), 134.6 (q, $^2J_{C\text{-}F}$ = 34.3 Hz, C_q), 134.5 (C_q), 133.1 (C_q), 131.4 (CH), 131.0 (CH), 129.9 (CH), 129.4 (CH), 128.6 (CH), 128.6 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 127.3 (C_q), 127.2 (CH), 125.4 (CH), 124.8 (CH), 123.5 (q, $^1J_{C\text{-}F}$ = 272.7 Hz, C_q), 122.9 (q, $^3J_{C\text{-}F}$ = 4.4 Hz, CH), 122.9 (q, $^3J_{C\text{-}F}$ = 4.4 Hz, CH), 119.1 (C_q). **^{19}F NMR** (283 MHz, $CDCl_3$) δ = – 63.08 (S). IR (ATR): 3055, 1669, 1433, 1314, 1277, 1168, 1129, 1065, 699 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 459 (10) [M+H$^+$], 442 (40), 413 (15), 353 (25), 338 (60), 181 (100), 78 (80). **HR-MS** (EI) *m/z* calcd for $C_{27}H_{17}F_3N_2O_2$ [M$^+$] 458.1242, found 458.1249.

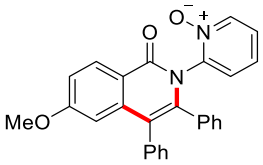


3, 4-Diphenyl-2-(pyridin-2-yl)-6-(trifluoromethyl) isoquinolin-1(2*H*)-one (134gd'):

M. p. = 203–205 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.65 (d, *J* = 8.4 Hz, 1H), 8.39 (ddd, *J* = 4.9, 1.9, 0.8 Hz, 1H), 7.70 (ddd, *J* = 8.4, 1.7, 0.6 Hz, 1H), 7.60 (dd, *J* = 7.8, 7.8 Hz 1H), 7.51 (m, 1H), 7.25–7.15 (m, 4H), 7.14–7.05 (m, 3H), 7.04–6.87 (m, 5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 161.8 (C_q), 152.3 (C_q), 149.2 (CH), 141.7 (C_q), 137.9 (C_q), 137.7 (CH), 135.0 (C_q), 134.3 (q, $^2J_{C\text{-}F}$ = 32.4 Hz, C_q), 133.8 (C_q), 131.4 (CH), 130.8 (CH), 129.2 (CH), 128.3 (CH), 127.7 (C_q), 127.6 (CH), 127.4 (CH), 127.2 (CH), 124.8 (CH), 123.7 (q, $^1J_{C\text{-}F}$ = 273.3 Hz, C_q), 123.1 (CH), 122.9 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, CH), 122.9 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, CH), 118.6 (C_q). **^{19}F NMR** (283 MHz, $CDCl_3$) δ = – 63.00 (S). IR (ATR): 1660, 1591, 1472, 1432, 1330, 1171, 1132, 1067, 756, 600 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 443 (30) [M+H$^+$], 442 (100) [M$^+$], 441 (35) [M–H$^+$], 413 (20), 365 (10), 337 (15), 78 (30). **HR-MS** (EI) *m/z* calcd for $C_{27}H_{17}F_3N_2O$ [M$^+$] 442.1293, found 442.1292.

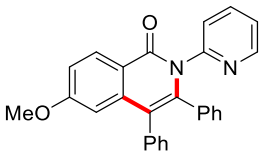
The general procedure **G** was followed, using amide **85b** (122 mg, 0.50 mmol) and alkyne **59d** (107 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1→CH_2Cl_2/acetone 1:1) yielded **134bd** (174 mg, 83%) and **134bd'** (26 mg, 13%) as colorless solids.

The general procedure **H** was followed, using amide **85b** (141 mg, 0.50 mmol) and alkyne **59d** (107 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **134bd'** (101 mg, 50%) as a colorless solid.



2-[6-Methoxy-1-oxo-3,4-diphenylisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134bd):

M. p. = 241–242 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.43 (d, *J* = 8.9 Hz, 1H), 8.11 (dd, *J* = 6.4, 1.4 Hz, 1H), 7.45–7.38 (m, 1H), 7.25–7.21 (m, 2H), 7.16–7.09 (m, 3H), 7.08–6.99 (m, 3H), 6.98–6.87 (m, 5H), 6.59 (d, *J* = 2.5 Hz, 1H), 3.69 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 163.4 (C_q), 161.1 (C_q), 145.6 (C_q), 140.3 (C_q), 140.2 (C_q), 139.7 (CH), 135.6 (C_q), 133.6 (C_q), 131.5 (CH), 131.2 (CH), 130.5 (CH), 130.0 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 127.1 (CH), 127.0 (CH), 125.2 (CH), 124.8 (CH), 119.1 (C_q), 118.8 (C_q), 115.3 (CH), 108.0 (CH), 55.3 (CH_3). **IR** (ATR): 3052, 1654, 1604, 1431, 1333, 1240, 860. cm^{-1}. **MS** (EI) *m/z* (relative intensity) 421 (10) [M+H$^+$], 420 (20) [M$^+$], 404 (100), 300 (80), 181 (90). **HR-MS** (ESI) *m/z* calcd for $C_{27}H_{21}N_2O_3$ [M+H$^+$] 421.1547, found 421.1545.

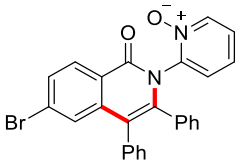


6-Methoxy-3,4-diphenyl-2-(pyridin-2-yl) isoquinolin-1(2*H*)-one (134bd'):

M. p. = 251–252 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.46 (d, *J* = 8.9 Hz, 1H), 8.34 (s_{br}, 1H), 7.55 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.21–7.15 (m, 3H), 7.14–7.09 (m, 3H), 7.06 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.02 (dd, *J* = 7.5, 4.8 Hz, 1H), 6.95 (s_{br}, 2H), 6.90–6.83 (m, 3H), 6.60 (d, *J* = 2.5 Hz, 1H), 3.68 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 163.0 (C_q), 162.2 (C_q), 152.7 (C_q), 148.9 (CH), 140.6 (C_q), 139.8 (C_q), 137.3 (CH), 136.1 (C_q), 134.4 (C_q), 131.5 (CH), 131.5 (CH), 130.2 (CH), 127.9 (CH), 127.2 (CH), 126.9 (CH), 126.8 (CH), 125.0 (CH), 122.7 (CH), 119.3 (C_q), 118.5 (C_q), 115.4 (CH), 107.6 (CH), 55.2 (CH_3). **IR** (ATR): 3058, 1654, 1589, 1432, 1325, 1288, 1026, 857, 758, 691 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 405 (40) [M+H$^+$], 404 (100) [M$^+$], 403 (40) [M–H$^+$], 375 (10), 181 (10), 152 (10), 78 (20). **HR-MS** (EI) *m/z* calcd for $C_{27}H_{20}N_2O_2$ [M$^+$] 404.1525, found 404.1514.

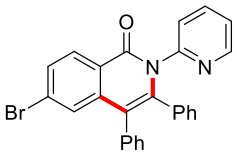
The general procedure **G** was followed, using amide **85d** (146 mg, 0.50 mmol) and alkyne **59d** (107 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1 → CH_2Cl_2/acetone 1:1) yielded **134dd** (143 mg, 61%) and **134dd'** (70 mg, 31%) as colorless solid.

The general procedure **H** was followed, using amide **85d** (146 mg, 0.50 mmol) and alkyne **59d** (107 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **134dd'** (120 mg, 53%) as colorless solid.



2-[6-Bromo-1-oxo-3, 4-diphenylisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134dd):

M. p. = 249–250 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.35 (d, *J* = 8.6 Hz, 1H), 8.14–8.09 (m, 1H), 7.58 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.43–7.35 (m, 2H), 7.30–7.23 (m, 1H), 7.22–7.14 (m, 3H), 7.14–7.09 (m, 1H), 7.08–7.01 (m, 2H), 7.01–6.86 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 161.0 (C_q), 145.3 (C_q), 141.1 (C_q), 139.8 (CH), 139.5 (C_q), 134.7 (C_q), 133.2 (C_q), 131.4 (CH), 131.1 (CH), 130.3 (CH), 130.1 (CH), 129.9 (CH), 128.6 (C_q), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.3 (CH), 127.2 (CH), 125.4 (CH), 124.9 (CH), 123.8 (C_q), 118.4 (C_q). **IR** (ATR): 3056, 1662, 1591, 1490, 1432, 1261, 701 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 470 (5) [M^+] (^{81}Br), 468 (5) [M^+] (^{79}Br), 350 (30) (^{81}Br), 348 (30) (^{79}Br), 269 (10), 239 (10), 181 (100). **HR-MS** (EI) *m/z* calcd for $C_{26}H_{17}{}^{79}BrN_2O_2$ [M^+] 468.0473, found 468.0475.

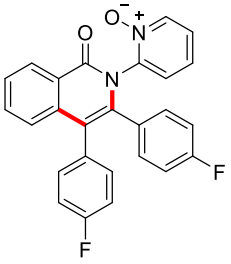


6-Bromo-3,4-diphenyl-2-(pyridin-2-yl) isoquinolin-1(2*H*)-one (134dd'):

M. p. = 243–245 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.40–8.36 (m, 2H), 7.62–7.55 (m, 2H), 7.37 (dd, *J* = 2.0, 0.5 Hz, 1H), 7.24–7.21 (m, 1H), 7.21–7.13 (m, 3H), 7.12–7.04 (m, 3H), 7.01–6.85 (m, 5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 162.2 (C_q), 152.4 (C_q), 149.1 (CH), 141.5 (C_q), 139.3 (C_q), 137.6 (CH), 135.3 (C_q), 135.3 (C_q), 134.0 (C_q), 131.5 (CH), 131.5 (CH), 130.2 (CH), 130.0 (CH), 128.2 (CH), 128.1 (CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 124.8 (CH), 124.3 (C_q), 123.0 (CH), 118.0 (C_q). **IR** (ATR): 3061, 1653, 1588, 1470, 1318, 1148, 924, 757, 701, 586 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 454 (75) [M^+] (^{81}Br), 452 (75) [M^+] (^{79}Br), 425 (10) (^{81}Br), 425 (10) (^{79}Br), 343 (10), 267 (10), 43 (100). **HR-MS** (EI) *m/z* calcd for $C_{26}H_{17}{}^{79}BrN_2O$ [M^+] 452.0524, found 452.0514.

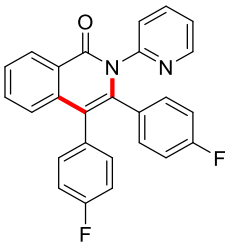
The general procedure **G** was followed, using amide **85a** (146 mg, 0.50 mmol) and alkyne **59o** (107 mg, 0.60 mmol) at 80 ºC for 16 h. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1 → CH_2Cl_2/acetone 1:1) yielded **134ao** (128 mg, 60%) and **134ao'** (60 mg, 29%) as colorless solids.

The general procedure **H** was followed, using amide **85a** (107 mg, 0.50 mmol) and alkyne **59o** (129 mg, 0.60 mmol) at 80 ºC for 16 h. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **134ao'** (160 mg, 78%) as a colorless solid.



2-[3, 4-Bis (4-fluorophenyl)-1-oxoisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134ao):

M. p. = 291–292 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.51 (dd, J = 7.9, 1.0 Hz, 1H), 8.13 (dd, J = 6.2, 1.2 Hz, 1H), 7.64–7.55 (m, 1H), 7.51 (ddd, J = 8.3, 7.2, 1.3 Hz, 1H), 7.47–7.40 (m, 1H), 7.22–7.11 (m, 3H), 7.11–7.00 (m, 3H), 6.99–6.81 (m, 3H), 6.70–6.62 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 162.2 (d, $^{1}J_{C\text{-}F}$ = 249.0 Hz, C_q), 161.7 (d, $^{1}J_{C\text{-}F}$ = 246.7 Hz, C_q), 161.3 (C_q), 145.2 (C_q), 139.8 (CH), 139.0 (C_q), 137.7 (C_q), 133.2 (CH), 133.1 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz, CH), 132.7 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz, CH), 131.8 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz, CH), 131.3 (d, $^{4}J_{C\text{-}F}$ = 3.5 Hz, C_q), 130.7 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz, CH), 129.4 (d, $^{4}J_{C\text{-}F}$ = 3.5 Hz, C_q), 128.4 (CH), 127.8 (CH), 127.2 (CH), 125.5 (CH), 125.4 (CH), 125.1 (C_q), 124.9 (CH), 118.7 (C_q), 115.4 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz, CH), 115.1 (d, $^{2}J_{C\text{-}F}$ = 21.5 Hz, CH), 115.0 (d, $^{2}J_{C\text{-}F}$ = 21.5 Hz, CH), 114.4 (d, $^{2}J_{C\text{-}F}$ = 21.8 Hz, CH). **^{19}F NMR** (283 MHz, $CDCl_3$) δ = – (111.4–111.5) (m), – (114.4–114.5) (m). **IR** (ATR): 3056, 1662, 1600, 1505, 1218, 1157, 774, 537 cm^{-1}. **MS** (EI) m/z (relative intensity) 411 (30) [M+H$^+$], 410 (100) [M$^+$], 409 (40) [M–H$^+$], 381 (40), 287 (20), 183 (10). **HR-MS** (EI) *m/z* calcd for $C_{26}H_{16}F_2N_2O$ [M$^+$] 410.1231, found 410.1219.



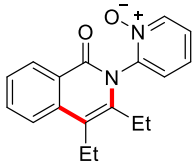
3, 4-Bis (4-fluorophenyl)-2-(pyridin-2-yl) isoquinolin-1(2*H*)-one (134ao'):

M. p. = 283–284 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.57–8.52 (m, 1H), 8.38 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H), 7.65–7.57 (m, 2H), 7.52 (ddd, J = 8.3, 7.2, 1.3 Hz, 1H), 7.23–7.20 (m, 2H), 7.13–7.06 (m, 3H), 6.97–6.86 (m, 4H), 6.64–6.59 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 162.4 (C_q), 161.7 (d, $^{1}J_{C\text{-}F}$ = 246.8 Hz, C_q), 161.4 (d, $^{1}J_{C\text{-}F}$ = 248.6 Hz, C_q), 152.5 (C_q), 149.1 (CH), 139.3 (C_q), 137.7 (CH), 137.5 (C_q), 133.0 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz, CH), 133.0 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz, CH), 132.8 (CH), 131.8 (d, $^{4}J_{C\text{-}F}$ = 3.5 Hz, C_q), 130.2 (d, $^{4}J_{C\text{-}F}$ = 3.6 Hz, C_q), 128.2 (CH), 127.1 (CH), 125.5 (C_q), 125.4 (CH), 124.8 (CH), 123.0 (CH), 118.2 (C_q), 115.2 (d, $^{2}J_{C\text{-}F}$ = 21.5 Hz, CH), 114.3 (d, $^{2}J_{C\text{-}F}$ = 21.6 Hz, CH). **^{19}F NMR** (376 MHz, $CDCl_3$) δ = – (112.8–112.9) (m), – (114.6–114.7) (m). **IR** (ATR): 3054, 1658, 1615, 1603, 1589, 1324, 1217, 1147, 836, 799 cm^{-1}. **MS** (EI) m/z (relative

intensity) 427 (5) [M+H$^+$], 426 (10) [M$^+$], 410 (20), 402 (10), 306 (60), 277 (20), 199 (100). **HR-MS** (EI) *m/z* calcd for $C_{26}H_{16}F_2N_2O_2$ [M$^+$] 426.1180, found 426.1189.

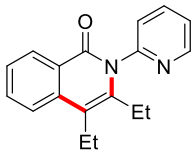
The general procedure **G** was followed, using amide **85a** (107 mg, 0.50 mmol) and alkyne **59p** (49 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1 → CH_2Cl_2/acetone 1:1) yielded **134ap** (84 mg, 57%) and **134ap'** (5 mg, 4%) as colorless solid.

The general procedure **H** was followed, using amide **85a** (107 mg, 0.50 mmol) and alkyne **59p** (49 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **134ap'** (86 mg, 62%) as a colorless solid.



2-[3, 4-Diethyl-1-oxoisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134ap):

M. p. = 195–196 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.37 (dd, *J* = 8.0, 8.0 Hz, 1H), 8.35–8.32 (m, 1H), 7.67 (d, *J* = 1.1 Hz, 1H), 7.66 (dd, *J* = 2.1, 1.1 Hz, 1H), 7.45–7.42 (m, 1H), 7.39 (ddd, *J* = 8.0, 5.2, 3.1 Hz, 1H), 7.35–7.32 (m, 2H), 2.76 (m, 2H), 2.65 (dd, *J* = 15.3, 7.6 Hz, 1H), 2.04 (dd, *J* = 15.3, 7.6 Hz, 1H), 1.24 (t, *J* = 7.6 Hz, 3H), 1.00 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 162.1 (C_q), 145.0 (C_q), 140.4 (CH), 139.6 (C_q), 137.3 (C_q), 133.0 (CH), 128.5 (CH), 128.0 (CH), 125.9 (CH), 125.9 (CH), 125.2 (CH), 125.1 (C_q), 122.9 (CH), 115.4 (C_q), 22.8 (CH_2), 20.3 (CH_2), 14.6 (CH_3), 13.6 (CH_3). **IR** (ATR): 3107, 2968, 1651, 1614, 1593, 1260, 784, 704 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 295 (5) [M+H$^+$], 294 (40) [M$^+$], 277 (100), 247 (70), 237 (20), 219 (20), 133 (90). **HR-MS** (EI) *m/z* calcd for $C_{18}H_{18}N_2O_2$ [M$^+$] 294.1368, found 294.1361.

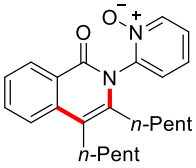


3, 4-Diethyl-2-(pyridin-2-yl) isoquinolin-1(2*H*)-one (134ap'):

M. p. = 114–115 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.67 (ddd, *J* = 4.7, 1.9, 1.0 Hz, 1H), 8.44 (ddd, *J* = 8.0, 1.5, 0.7 Hz, 1H), 7.89 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.74–7.66 (m, 2H), 7.46–7.37 (m, 3H), 2.81 (q, *J* = 7.5 Hz, 2H), 2.41 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.5 Hz, 3H), 1.01 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 163.0 (C_q), 152.9 (C_q), 149.6 (CH), 140.1 (C_q), 138.1 (CH), 137.0 (C_q), 132.6 (CH), 128.3 (CH), 125.8 (CH), 125.4 (C_q), 124.6 (CH), 123.6 (CH), 122.7 (CH), 114.8 (C_q), 22.9 (CH_2), 20.2 (CH_2), 14.6 (CH_3), 13.7 (CH_3). **IR** (ATR): 3064, 2976, 1650, 1465, 1327, 993, 897, 775, 676 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 279 (10) [M+H$^+$], 278 (50) [M$^+$], 277 (100) [M–H$^+$], 263 (30), 249 (40), 247 (30), 234 (15). **HR-MS** (ESI) *m/z* calcd for $C_{18}H_{18}N_2NaO$ [M+Na$^+$] 301.1311, found 301.1314.

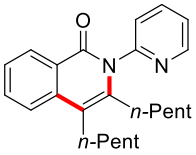
The general procedure **G** was followed, using amide **85a** (107 mg, 0.50 mmol) and alkyne **59q** (100 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1 → CH_2Cl_2/acetone 1:1) yielded **134aq** (85 mg, 45%) and **134aq'** (31 mg, 17%) as colorless solids.

The general procedure **H** was followed, using amide **85a** (107 mg, 0.50 mmol) and alkyne **59q** (100 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **134aq'** (110 mg, 61%) as a colorless solid.



2-[1-Oxo-3, 4-di-*n*-pentylisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134aq):

M. p. = 121–122 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.42–8.37 (m, 2H), 7.74–7.64 (m, 2H), 7.51–7.41 (m, 2H), 7.41–7.34 (m, 2H), 2.81–2.53 (m, 3H), 2.03–1.93 (m, 1H), 1.71–1.57 (m, 2H), 1.54–1.24 (m, 6H), 1.19–1.03 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.78 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 162.2 (C_q), 145.2 (C_q), 140.5 (CH), 138.8 (C_q), 137.6 (C_q), 133.0 (CH), 128.6 (CH), 128.2 (CH), 125.9 (CH), 125.8 (CH), 125.1 (CH), 125.1 (C_q), 123.0 (CH), 114.6 (C_q), 32.2 (CH_2), 31.7 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 28.7 (CH_2), 27.5 (CH_2), 22.5 (CH_2), 21.8 (CH_2), 14.0 (CH_3), 13.8 (CH_3). **IR** (ATR): 2957, 2923, 2855, 1651, 1592, 1426, 1259, 765, 703 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 379 (5) [M+H$^+$], 378 (30) [M$^+$], 361 (80), 321 (20), 307 (30), 251 (100), 247 (50). **HR-MS** (EI) *m/z* calcd for $C_{24}H_{30}N_2O_2$ [M$^+$] 378.2307, found 378.2301.

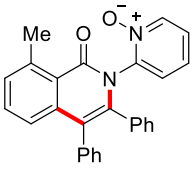


3, 4-Di-*n*-pentyl-2-(pyridin-2-yl) isoquinolin-1 (2*H*)-one (134aq'):

M. p. = 104–105 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.67 (dd, *J* = 5.4, 1.8 Hz, 1H), 8.43 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.88 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.72–7.65 (m, 2H), 7.46–7.37 (m, 3H), 2.75–2.69 (m, 2H), 2.40–2.24 (m, 2H), 1.63 (m, 2H), 1.52–1.34 (m, 6H), 1.10–1.07 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H), 0.76 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 163.0 (C_q), 152.9 (C_q), 149.5 (CH), 139.2 (C_q), 138.0 (CH), 137.3 (C_q), 132.5 (CH), 128.3 (CH), 125.7 (CH), 125.3 (C_q), 124.7 (CH), 123.5 (CH), 122.8 (CH), 113.9 (C_q), 32.2 (CH_2), 31.7 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 28.6 (CH_2), 27.3 (CH_2), 22.4 (CH_2), 21.7 (CH_2), 14.0 (CH_3), 13.7 (CH_3). **IR** (ATR): 2926, 2868, 1651, 1555, 1486, 1325, 995, 768, 695 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 363 (15) [M+H$^+$], 362 (65) [M$^+$], 361 (80) [M–H$^+$], 319 (55), 305 (100), 291 (40), 247 (40). **HR-MS** (ESI) *m/z* calcd for $C_{24}H_{29}N_2O$ [M–H$^+$] 361.2280, found 361.2271.

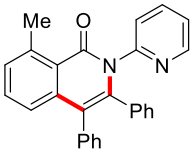
The general procedure **G** was followed, using amide **85i** (114 mg, 0.50 mmol) and alkyne **59d** (107 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1 → CH_2Cl_2/acetone 1:1) and then by GPC yielded **134id'** (66 mg, 34%) and **134id** (59 mg, 29%) as colorless solids.

The general procedure **H** was followed, using amide **85i** (114 mg, 0.50 mmol) and alkyne **59d** (107 mg, 0.60 mmol), Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **134id'** (150 mg, 77%) as a colorless solid.



2-[8-Methyl-1-oxo-3, 4-diphenylisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134id):

M. p. = 272–273 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.16–8.11 (m, 1H), 7.48–7.41 (m, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.30–7.19 (m, 3H), 7.18–7.09 (m, 3H), 7.08–6.98 (m, 4H), 6.97–6.85 (m, 4H), 2.94 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 162.1 (C_q), 146.0 (C_q), 142.7 (C_q), 139.8 (CH), 139.7 (C_q), 139.5 (C_q), 136.3 (C_q), 133.6 (C_q), 132.2 (CH), 131.6 (CH), 131.4 (CH), 130.2 (CH), 130.0 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 128.0 (CH), 127.8 (CH), 127.6 (CH), 127.0 (CH), 126.9 (CH), 125.0 (CH), 124.7 (CH), 124.2 (CH), 123.5 (C_q), 119.5 (C_q), 24.1 (CH_3). **IR** (ATR): 3053, 2920, 1660, 1590, 1488, 1339, 1304, 1275, 808, 744 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 405 (5) [M+H$^+$], 404 (20) [M$^+$], 388 (40), 371 (20), 359 (20), 310 (10), 284 (50), 284 (50), 181 (100). **HR-MS** (ESI) *m/z* calcd for $C_{27}H_{21}N_2O_2$ [M+H$^+$] 405.1598, found 405.1594.

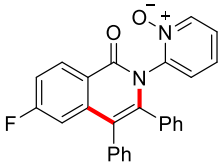


8-Methyl-3, 4-diphenyl-2-(pyridin-2-yl) isoquinolin-1(2*H*)-one (134id'):

M. p. = 281–283 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.40 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.58–7.53 (m, 1H), 7.39 (dd, *J* = 8.2, 8.2 Hz, 1H), 7.25 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.21–7.09 (m, 6H), 7.08–7.02 (m, 2H), 6.98–6.84 (m, 5H), 2.96 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 163.5 (C_q), 153.2 (C_q), 149.1 (CH), 142.4 (C_q), 139.9 (C_q), 139.5 (C_q), 137.5 (CH), 136.7 (C_q), 134.3 (C_q), 131.8 (CH), 131.6 (CH), 131.6 (CH), 130.1 (CH), 127.9 (CH), 127.1 (CH), 126.9 (CH), 126.7 (CH), 125.0 (CH), 124.0 (CH), 123.9 (C_q), 122.7 (CH), 118.9 (C_q), 24.2 (CH_3). **IR** (ATR): 3059, 2923, 1653, 1557, 1488, 1434, 1149, 997, 695, 593 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 389 (30) [M+H$^+$], 388 (100) [M$^+$], 387 (40) [M–H$^+$], 371 (20), 359 (20), 310 (10), 78 (15). **HR-MS** (EI) *m/z* calcd for $C_{27}H_{20}N_2O$ [M$^+$] 388.1576, found 388.1589.

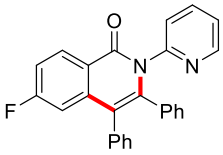
The general procedure **G** was followed, using amide **85h** (116 mg, 0.50 mmol) and alkyne **59d** (107 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1 → CH_2Cl_2/acetone 1:1) yielded **134hd** (131 mg, 64%) and **134hd'** (49 mg, 25%) as colorless solids.

The general procedure **H** was followed, using amide **85h** (116 mg, 0.50 mmol) and alkyne **59d** (107 mg, 0.60 mmol), Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **134hd'** (108 mg, 55%) as colorless solid.



2-[6-Fluoro-1-oxo-3, 4-diphenylisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134hd):

M. p. = 243–244 ºC **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.53 (dd, J = 8.9, 5.9 Hz, 1H), 8.14 (dd, J = 6.5, 1.4 Hz, 1H), 7.46–7.38 (m, 1H), 7.30–7.24 (m, 1H), 7.24–7.21 (m, 1H), 7.21–7.15 (m, 3H), 7.15–7.03 (m, 3H), 7.03–6.93 (m, 4H), 6.92–6.83 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 165.8 (d, $^1J_{C\text{-}F}$ = 252.9 Hz, C_q), 160.7 (C_q), 141.1 (C_q), 140.7 (d, $^3J_{C\text{-}F}$ = 9.9 Hz, C_q), 139.8 (CH), 135.0 (C_q), 133.3 (C_q), 131.6 (d, $^3J_{C\text{-}F}$ = 10.1 Hz, CH), 131.4 (CH), 131.1 (CH), 129.9 (CH), 128.5 (CH), 128.5 (CH), 128.4 (CH), 127.9 (CH), 127.9 (CH), 127.8 (CH), 127.3 (CH), 127.1 (CH), 125.3 (CH), 124.7 (CH), 121.7 (C_q), 121.7 (C_q), 118.9 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, C_q), 115.5 (d, $^2J_{C\text{-}F}$ = 23.4 Hz, CH), 111.2 (d, $^2J_{C\text{-}F}$ = 23.4 Hz, CH). **^{19}F NMR** (282 MHz, $CDCl_3$) δ = – 104.10 (ddd, J = 10.4, 8.3, 5.9 Hz). **IR** (ATR): 3063, 1664, 1608, 1472, 1434, 1328, 1259, 868, 759, 712 cm^{-1}. **HR-MS** (ESI) m/z calcd for $C_{26}H_{18}F_1N_2O_2$ [M+H$^+$] 409.1347, found 409.1346.

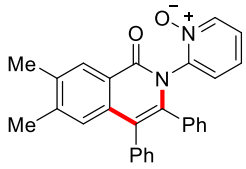


6-Fluoro-3,4-diphenyl-2-(pyridin-2-yl) isoquinolin-1(2*H*)-one (134hd'):

M. p. = 206–208 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.54 (dd, J = 8.8, 5.9 Hz, 1H), 8.37 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H), 7.58 (dd, J = 7.6, 7.6, 1H), 7.23–7.14 (m, 5H), 7.13–7.05 (m, 3H), 7.00–6.83 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 165.6 (d, $^1J_{C\text{-}F}$ = 254.7 Hz, C_q), 161.9 (C_q), 152.5 (C_q), 149.1 (CH), 141.4 (C_q), 140.4 (d. $^3J_{C\text{-}F}$ = 9.8 Hz, C_q), 137.6 (CH), 135.5 (C_q), 134.0 (C_q), 131.4 (CH), 131.4 (CH), 131.3 (d, $^3J_{C\text{-}F}$ = 8.4 Hz, CH), 128.2 (CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 124.9 (CH), 123.0 (CH), 122.1 (d, $^4J_{C\text{-}F}$ = 1.7 Hz, C_q), 118.4 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, C_q), 115.5 (d, $^2J_{C\text{-}F}$ = 23.6 Hz, CH) 111.9 (d, $^2J_{C\text{-}F}$ = 23.4 Hz, CH). **^{19}F NMR** (283 MHz, $CDCl_3$) δ = – 105.03 (ddd, J = 10.5, 8.1, 6.0 Hz). **IR** (ATR): 3057, 1659, 1612, 1470, 1436, 1323, 1181, 950, 785, 701 cm^{-1}. **MS** (EI) m/z (relative intensity) 393 (30) [M+H$^+$], 392 (100) [M$^+$], 391 (50) [M–H$^+$], 363 (20), 287 (15), 181 (10), 78 (20). **HR-MS** (EI) m/z calcd for $C_{26}H_{17}FN_2O$ [M$^+$] 392.1325, found 392.1325.

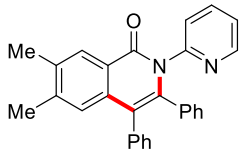
The general procedure **G** was followed, using amide **85j** (121 mg, 0.50 mmol) and alkyne **59d** (107 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1 → CH_2Cl_2/acetone 1:1) yielded **134jd** (168 mg, 80%) and **134jd'** (29 mg, 14%) as colorless solids.

When The general procedure **H** was followed, using amide **85j** (121 mg, 0.50 mmol), alkyne **59d** (107 mg, 0.60 mmol), purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **134jd'** (157 mg, 78%) as a colorless solid.



2-[6, 7-Dimethyl-1-oxo-3, 4-diphenylisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134jd):

M. p. = 272–273 °C **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.26 (s, 1H), 8.11 (dd, J = 6.4, 1.5 Hz, 1H), 7.44–7.38 (m, 1H), 7.24–7.19 (m, 1H), 7.18–7.08 (m, 3H), 7.07–6.98 (m, 3H), 6.98–6.86 (m, 6H), 2.37 (s, 3H), 2.25 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 161.4 (C_q), 145.8 (C_q), 143.1 (C_q), 139.8 (CH), 138.8 (C_q), 136.5 (C_q), 136.1 (C_q), 135.9 (C_q), 133.8 (C_q), 131.6 (CH), 131.3 (CH), 130.2 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.2 (CH), 128.0 (CH), 127.8 (CH), 127.6 (CH), 127.0 (CH), 126.9 (CH), 126.1 (CH), 125.1 (CH), 124.7 (CH), 123.1 (C_q), 119.2 (C_q), 20.4 (CH_3), 19.7 (CH_3). **IR** (ATR): 3054, 2234, 1651, 1591, 1487, 1331, 1264, 752 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 418 (10) [M^+], 402 (20), 313 (25), 298 (40), 181 (100). **HR-MS** (ESI) *m/z* calcd for $C_{28}H_{22}N_2O_2$ [M^+] 418.1681, found 418.1672.

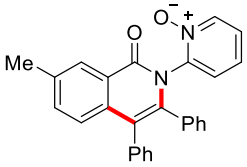


6, 7-Dimethyl-3, 4-diphenyl-2-(pyridin-2-yl) isoquinolin-1(2*H*)-one (134jd'):

M. p. = 240–241 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.39–8.35 (m, 1H), 8.30 (s, 1H), 7.58 (dd, J = 7.7, 7.7 Hz, 1H), 7.25–7.10 (m, 6H), 7.08–7.03 (m, 1H), 7.00–6.92 (m, 3H), 6.89–6.86 (m, 3H), 2.41 (s, 3H), 2.28 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 162.5 (C_q), 152.9 (C_q), 148.9 (CH), 142.6 (C_q), 139.1 (C_q), 137.4 (CH), 136.4 (C_q), 136.3 (C_q), 135.9 (C_q), 134.5 (C_q), 131.6 (CH), 131.0 (CH), 128.2 (CH), 127.8 (CH), 127.1 (CH), 126.9 (CH), 126.7 (CH), 126.0 (CH), 125.0 (CH), 123.6 (C_q), 122.7 (CH), 118.7 (C_q), 20.4 (CH_3), 19.7 (CH_3). **IR** (ATR): 3054, 2918, 1659, 1617, 1586, 1487, 1465, 1431, 1321, 715 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 403 (35) [M+H^+], 402 (100) [M^+], 401 (30) [M–H^+], 373 (20), 297 (15), 181 (10). **HR-MS** (ESI) *m/z* calcd for $C_{28}H_{22}N_2O$ [M^+] 402.1732, found 402.1723.

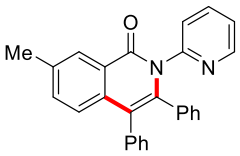
The general procedure **G** was followed, using amide **85k** (114 mg, 0.50 mmol) and alkyne **59d** (107 mg, 0.60 mmol). Purification by column chromatography on silica gel (n-hexane/EtOAc 2:1 → CH_2Cl_2/acetone 1:1) and then by GPC yielded **134kd** (144 mg, 71%) and **134kd'** (45 mg, 23%) as colorless solids.

The general procedure **H** was followed, using amide **85k** (114 mg, 0.50 mmol) and alkyne **59d** (107 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **134kd'** (172 mg, 78%) as a colorless solid**.**



2-(7-Methyl-1-oxo-3, 4-diphenylisoquinolin-2(1*H*)-yl) pyridine 1-oxide (134kd):

M. p. = 161–162 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.32 (dd, *J* = 1.2, 0.6 Hz, 1H), 8.13 (d, *J* = 6.4 Hz, 1H), 7.44–7.38 (m, 2H), 7.27–7.20 (m, 2H), 7.16–7.10 (m, 4H), 7.07–7.03 (m, 2H), 7.01 – 6.94 (m, 3H), 6.93–6.88 (m, 2H), 2.47 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 161.5 (C_q), 139.9 (CH), 138.7 (C_q), 137.2 (C_q), 137.2 (C_q), 135.8 (C_q), 135.7 (C_q), 134.5 (CH), 133.7 (C_q), 131.6 (CH), 131.3 (CH), 130.2 (CH), 128.7 (CH), 128.3 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.1 (CH), 127.0 (CH), 125.8 (CH), 125.2 (CH), 125.0 (C_q), 124.7 (CH), 119.4 (C_q), 21.3 (CH_3). **IR** (ATR): 3053, 3002, 2918, 1655, 1593, 1510, 1488, 1436, 1243, 761 cm^{-1}. **HR-MS** (ESI) *m/z* calcd for $C_{27}H_{21}N_2O_2$ [M+H$^+$] 405.1598, found 405.1601.

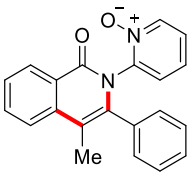


7-Methyl-3, 4-diphenyl-2-(pyridin-2-yl)isoquinolin-1(2*H*)-one (134kd'):

M. p. = 180–181 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.40–8.31 (m, 2H), 7.57 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.39 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.22–7.02 (m, 8H), 6.99–6.81 (m, 5H), 2.48 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 162.6 (C_q), 152.8 (C_q), 149.0 (CH), 139.1 (C_q), 137.4 (CH), 137.0 (C_q), 136.3 (C_q), 135.5 (C_q), 134.4 (C_q), 134.1 (CH), 131.6 (CH), 131.6 (CH), 127.9 (CH), 127.7 (CH), 127.1 (CH), 127.0 (CH), 126.8 (CH), 125.6 (CH), 125.4 (C_q), 125.0 (CH), 122.8 (CH), 118.9 (C_q), 21.3 (CH_3). **IR** (ATR): 3055, 2919, 1654, 1587, 1432, 1316, 997, 833, 760 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 389 (30) [M+H$^+$], 388 (100) [M$^+$], 387 (30) [M–H$^+$], 359 (20), 283 (15), 181 (10), 78 (30). **HR-MS** (EI) *m/z* calcd for $C_{27}H_{20}N_2O$ [M$^+$] 388.1576, found 388.1587.

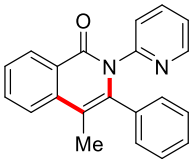
The general procedure **G** was followed, using amide **85a** (107 mg, 0.50 mmol) and alkyne **59b** (70 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1 → CH_2Cl_2/acetone 1:1) yielded **134ab** (13:1 mixture of isomers, only the major isomer could be isolated by column chromatography) (120 mg, 73%) and **134ab'** (5 mg, 3%) as colorless solids.

The general procedure **H** was followed, using amide **85a** (107 mg, 0.50 mmol) and alkyne **59b** (70 mg, 0.60 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **134ab'** (16:1 mixture of isomers, only the major isomer could be isolated by column chromatography) (114 mg, 73%) as a colorless solid.



2-[4-Methyl-1-oxo-3-phenylisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134ab):

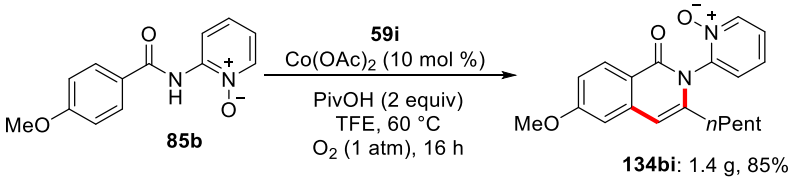
M. p. = 227–228 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.48 (dt, J = 8.0, 1.0 Hz, 1H), 8.11–8.05 (m, 1H), 7.78–7.68 (m, 2H), 7.55–7.46 (m, 2H), 7.26–7.11 (m, 4H), 7.09–6.93 (m, 3H), 2.08 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 161.3 (C_q), 145.6 (C_q), 139.7 (CH), 138.5 (C_q), 137.9 (C_q), 133.9 (C_q), 133.1 (CH), 129.7 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 126.8 (CH), 125.3 (C_q), 125.1 (CH), 124.5 (CH), 123.6 (CH), 111.2 (C_q), 14.6 (CH_3). **IR** (ATR): 3048, 1652, 1622, 1590, 1489, 1430, 1337, 1263, 761 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 329 (5) [M+H$^+$], 328 (20) [M$^+$], 312 (10), 283 (10), 208 (50), 193 (25), 181 (100), 165 (20). **HR-MS** (EI) *m/z* calcd for $C_{21}H_{16}N_2O_2$ [M$^+$] 328.1212, found 328.1224.



4-Methyl-3-phenyl-2-(pyridin-2-yl) isoquinolin-1(2*H*)-one (134ab'):

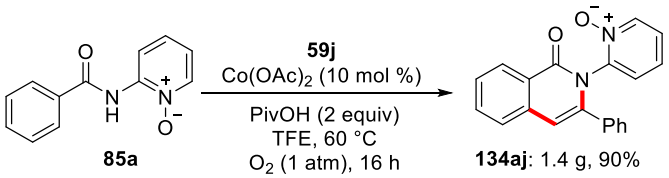
M. p. = 162–163 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.54 (dd, J = 8.0, 8.0 Hz, 1H), 8.37–8.34 (m, 1H), 7.78–7.73 (m, 2H), 7.59 –7.55 (m, 1H), 7.55–7.51 (m, 1H), 7.21–7.09 (m, 6H), 7.06–7.02 (m, 1H), 2.11 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 162.4 (C_q), 152.8 (C_q), 148.9 (CH), 139.1 (C_q), 137.7 (C_q), 137.3 (CH), 134.7 (C_q), 132.7 (CH), 130.5 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 126.7 (CH), 125.8 (C_q), 124.9 (CH), 123.4 (CH), 122.6 (CH), 110.5 (C_q), 14.5 (CH_3). **IR** (ATR): 3059, 2917, 1650, 1586, 1483, 1463, 1324, 776, 688 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 313 (25) [M+H$^+$], 312 (100) [M$^+$], 311 (45) [M–H$^+$], 283 (70), 269 (30), 206 (15). **HR-MS** (EI) *m/z* calcd for $C_{21}H_{16}N_2O$ [M$^+$] 312.1263, found 312.1260.

Procedure for Gram-Scale Reactions



To a 50 mL Schlenk flask was added amide **85b** (1.22 g, 5.0 mmol), alkyne **59i** (577 mg, 6.0 mmol), PivOH (1.02 g, 10.0 mmol), $Co(OAc)_2$ (88 mg, 10 mol %). The Schlenk flask was evacuated and refilled with O_2 three times with a balloon. TFE (20 mL) was added *via* cannula and the mixture was stirred in a pre-heated (60 ºC) oil bath for 16 h (The O_2 balloon was connected to the Schlenk flask until the reaction was finished). At ambient temperature, the reaction was stopped by adding saturated aqueous $NaHCO_3$ (40 mL). The mixture was extracted with CH_2Cl_2 (4×30 mL) and the organic phase dried over Na_2SO_4. Evaporation of the solvent

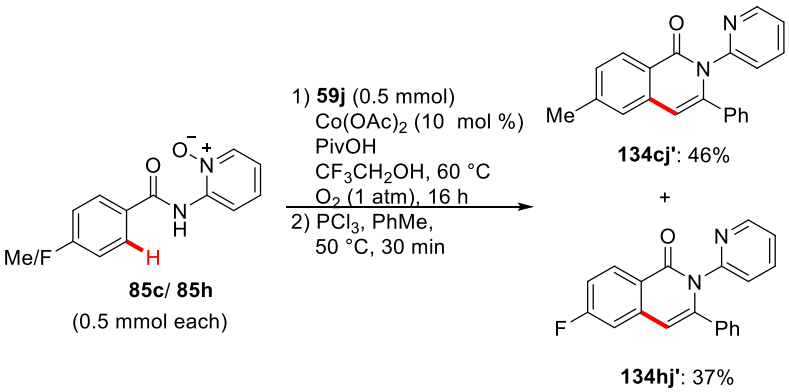
and purification by column chromatography on silica gel (CH_2Cl_2/acetone 3:1) afforded the corresponding product **134bi** (1.44 g, 85%) as a colorless solid.



To a 50 mL Schlenk flask was added aromatic amides **85a** (1.07 g, 5.0 mmol), alkyne **59j** (613 mg, 6.0 mmol), PivOH (1.02 g, 10.0 mmol), $Co(OAc)_2$ (88 mg, 10 mol %). The Schlenk flask was evacuated and refilled with O_2 three times with a balloon. TFE (20 mL) was added *via* cannula and the mixture was stirred in a pre-heated (60 ºC) oil bath for 16 h (The O_2 balloon was connected to the Schlenk flask until the reaction was finished). At ambient temperature, the reaction was stopped by adding saturated aqueous $NaHCO_3$ (40 mL). The mixture was extracted with CH_2Cl_2 (4×30 mL) and the organic phase dried over Na_2SO_4. Evaporation of the solvents and purification by column chromatography on silica gel (CH_2Cl_2/acetone 3:1) afforded the corresponding product **134aj** (1.41 g, 90%) as a colorless solid.

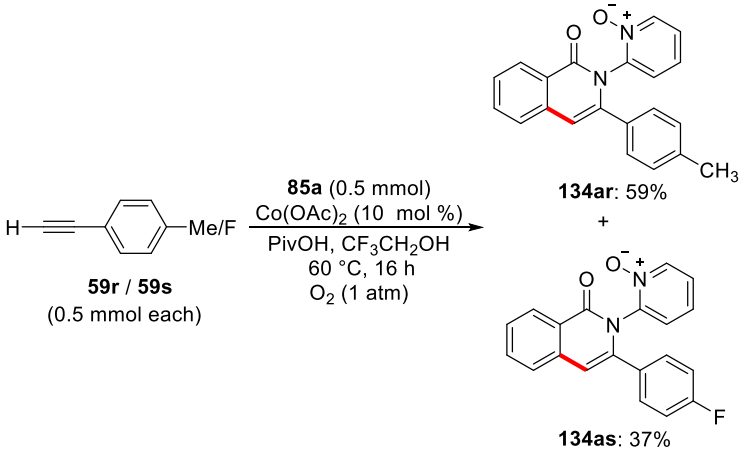
Intermolecular Competition Experiments

1) Intermolecular Competition Experiment between aromatic amides 85c and 85h.



The general procedure **H** was followed, using amides **85c** (114 mg, 0.50 mmol), **85h** (116 mg, 0.50 mmol) and alkyne **59j** (51 mg, 0.50 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc) gave a mixture (133 mg) of **134cj'** (46%) and **134hj'** (37%) as a colorless solid.

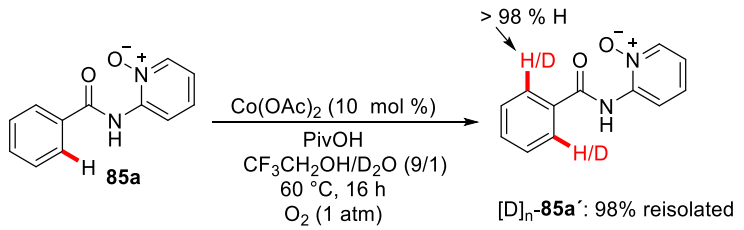
2) Intermolecular Competition Experiment between alkyne 59r and 59s.



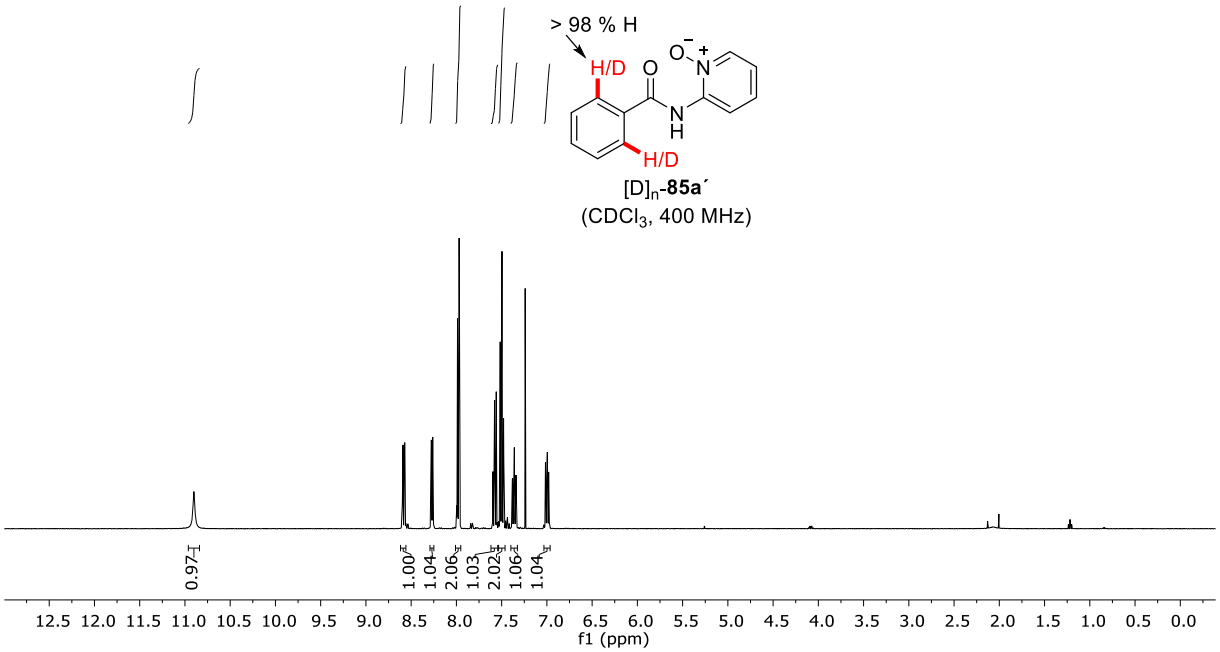
The general procedure **G** was followed, using amide **85a** (107 mg, 0.50 mmol) and alkynes **59r** (58 mg, 0.50 mmol) and **59s** (60 mg, 0.50 mmol). Purification by column chromatography on silica gel (CH_2Cl_2/acetone 2:1) gave a mixture (159 mg) of **134ar** (59%) and **134as** (37%) as a colorless solid.

H/D Exchange Experiment

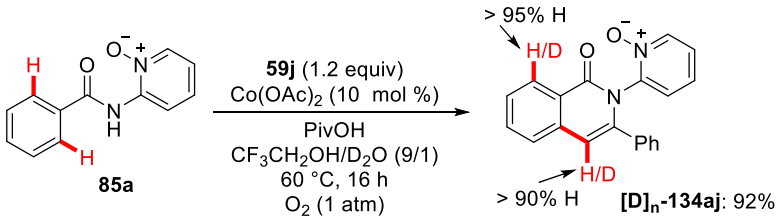
1) Cobalt-Catalyzed H/D Exchange in Substrate 85a with D_2O as the Co-solvent in the Absence of Alkyne



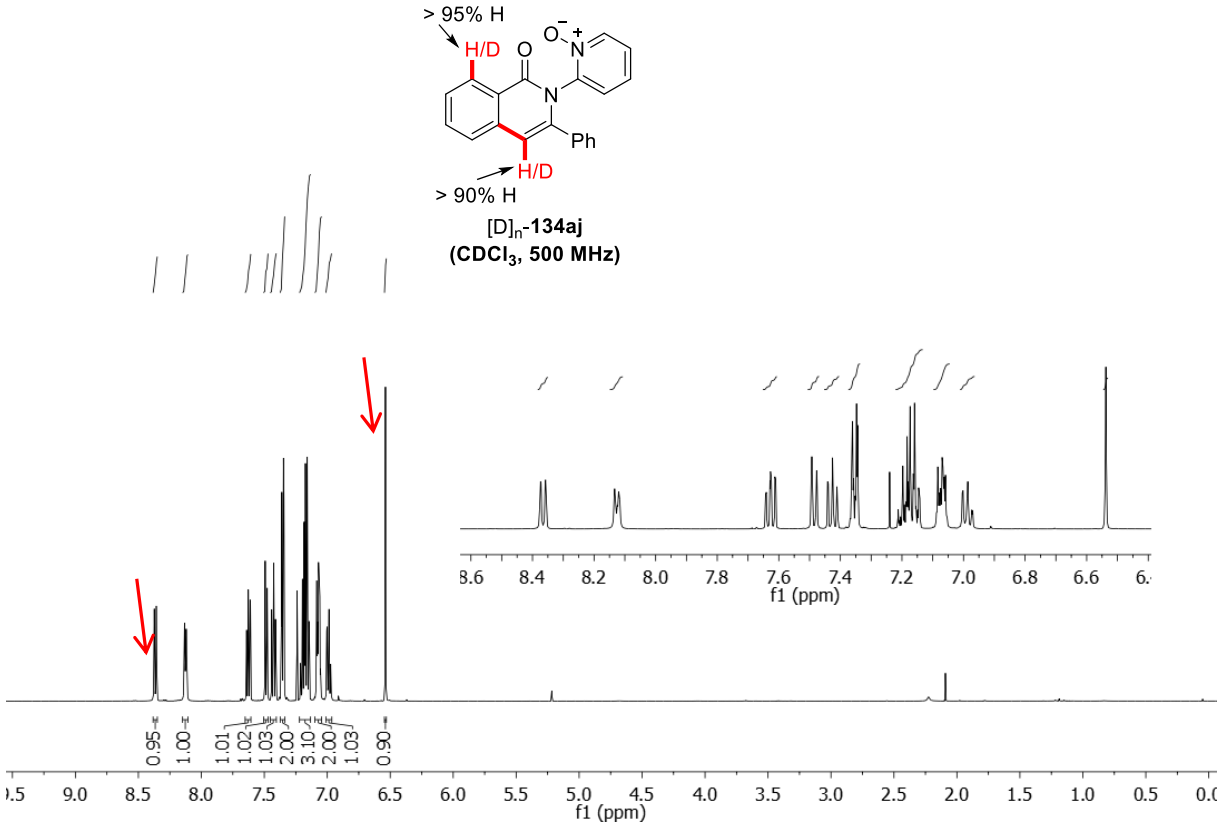
Under an atmosphere of ambient air, to a 25 mL Schlenk tube were added amide **85a** (107 mg, 0.50 mmol), PivOH (102 mg, 1.0 mmol), $Co(OAc)_2$ (8.9 mg, 10 mol %). The Schlenk tube was evacuated and refilled with O_2 three times with a balloon. TFE (1.8 mL) and D_2O (0.2 mL) was added *via* cannula. Then the mixture was stirred in a pre-heated (60 ºC) oil bath for 16 h (The O_2 balloon was connected to the Schlenk tube until the reaction was finished). At ambient temperature, the reaction was stopped by adding saturated aqueous $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (4×10 mL) and dried over Na_2SO_4. Evaporation of the solvents and purification by column chromatography on silica gel (CH_2Cl_2/acetone 2:1) gave $[D]_n$-**85a´** (105 mg, 98%) as a colorless solid. The D-incorporation was estimated based on ^{1}H-NMR spectroscopy.



2) Cobalt-Catalyzed H/D Exchange with D_2O as the Co-solvent in the Presence of Alkyne 59j

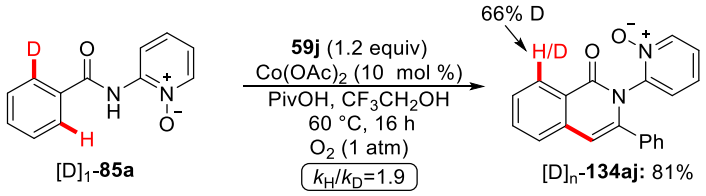


The general procedure **G** was followed, using **85a** (107 mg, 0.50 mmol), **59j** (61 mg, 0.60 mmol), $Co(OAc)_2$ (9.0 mg, 10 mol %) and PivOH (102 mg, 1.0 mmol) in a solvent mixture of CF_3CH_2OH (1.8 mL) and CD_3OD(0.2 mL). Purification by column chromatography (CH_2Cl_2 /acetone: 2:1→1:1) yielded $[D]_n$-**134aj** (145 mg, 92%) as a colorless solid. The D-incorporation was estimated by ^{1}H-NMR spectroscopy.

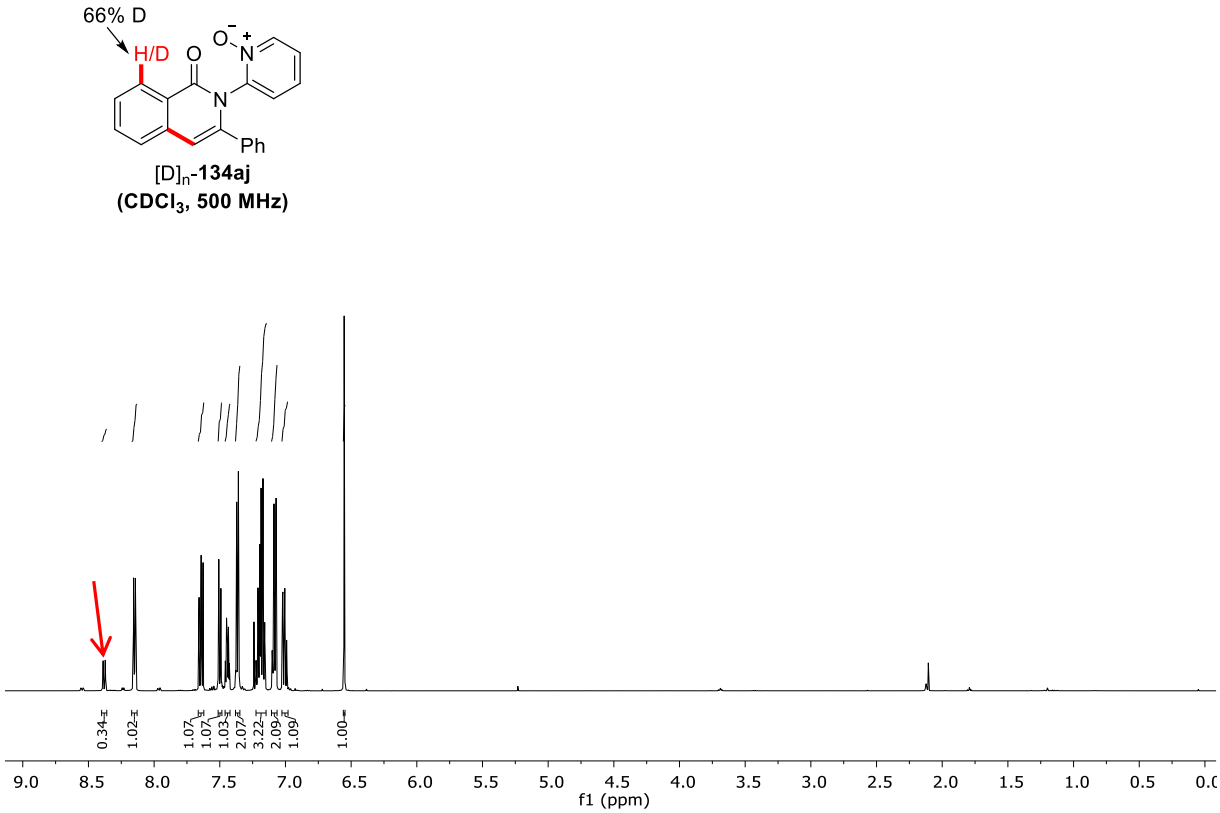


Kinetic Isotope Effect Experiments

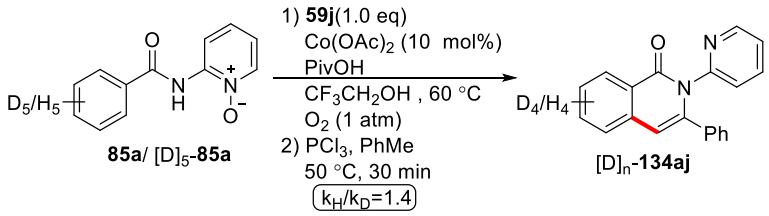
1) Intramolecular Competition Experiment



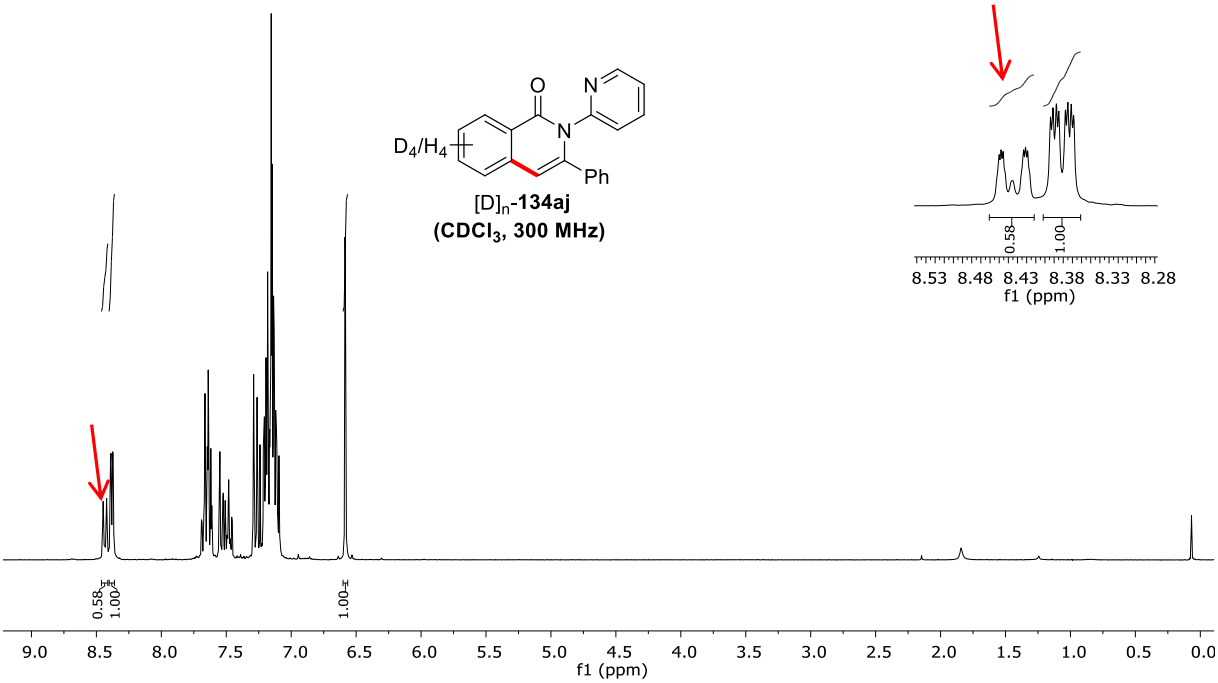
The general procedure **G** was followed, using $[D]_1$-**85a** (107 mg, 0.50 mmol) and **59j** (61 mg, 0.60 mmol). Purification by column chromatography (CH_2Cl_2/acetone: 2:1→1:1) yielded $[D]_n$-**134aj** (127 mg, 81%) as a colorless solid. The D-incorporation in $[D]_n$-**134aj** was estimated by ^{1}H-NMR spectroscopy.



2) Intermolecular Competition Experiment

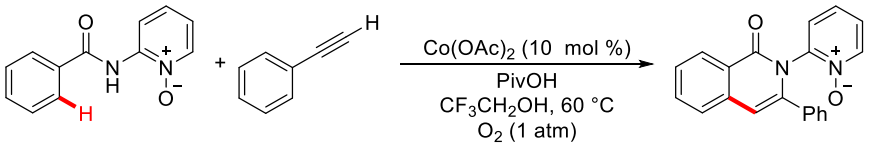


The general procedure **H** was followed, using aromatic amide **85a** (107 mg, 0.50 mmol), $[D]_5$-**85a** (109 mg, 0.50 mmol) and alkyne **59j** (51 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane /EtOAc 2:1→1:1) yielded a mixture of **134aj** and $[D]_4$-**134aj** (92 mg, 61%) as a colorless solid. The D-incorporation in $[D]_n$-**134aj** was estimated by ^{1}H-NMR spectroscopy.



Oxygen up-take Studies

1) **O_2-uptake Study with Terminal Alkyne 2a**



85a **59j** **134aj**: 96%

The general procedure **G** was followed, using aromatic amide **85a** (200 mg, 0.93 mmol), alkyne **59j** (114 mg, 1.12 mmol), PivOH (190 mg, 1.86 mmol) and $Co(OAc)_2$ (16.5 mg, 10 mol %). The Schlenk tube was connected to a burette with a reservoir filled with oxygen-saturated water. The mixture was stirred at 60 ºC and the changes in volume were determined, as shown in Table S-2. At ambient temperature, the reaction was stopped by adding saturated aqueous $NaHCO_3$ (30 mL). This mixture was extracted with CH_2Cl_2 (4×20 mL) and dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography on silica gel (CH_2Cl_2/acetone 2:1) yielded **134aj** (291 mg, 96%) as a colorless solid.

Table S-1: O_2-uptake Study.

t / h	V / mL	ΔV / mL	n / mmol
0	21.7	0	0
0.083	21.8	0	0
0.167	21.7	0	0
0.217	21.4	0.3	0.013
0.250	21.1	0.6	0.027
0.283	21.0	0.7	0.031
0.333	20.7	1.0	0.045
0.417	19.8	1.9	0.085
0.500	19.0	2.7	0.120
0.583	18.5	3.2	0.143
0.667	17.9	3.8	0.170
0.750	17.6	4.1	0.183
0.833	17.4	4.3	0.192
0.917	17.2	4.5	0.201
1.000	17.0	4.7	0.210
1.083	16.7	5.0	0.223
1.167	16.5	5.2	0.232
1.333	16.0	5.7	0.254
1.500	15.7	6.0	0.268
1.667	15.4	6.3	0.281
1.833	15.0	6.7	0.299
2.000	14.8	6.9	0.308
2.167	14.3	7.4	0.330
2.500	13.7	8.0	0.357
2.833	12.9	8.8	0.393
3.167	12.5	9.2	0.411
3.500	12.3	9.4	0.420
3.750	12.0	9.7	0.433
4.667	11.0	10.7	0.478
5.000	10.8	10.9	0.486
5.417	10.7	11.0	0.491
6.000	10.8	10.9	0.487
6.250	10.8	10.9	0.487

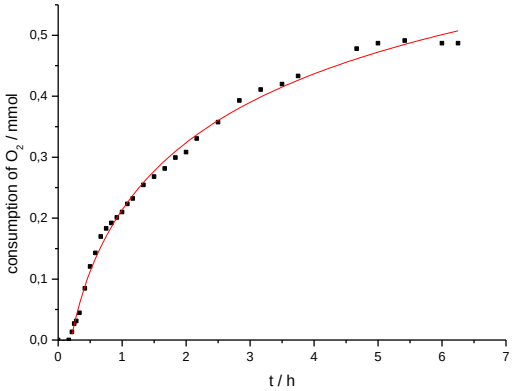
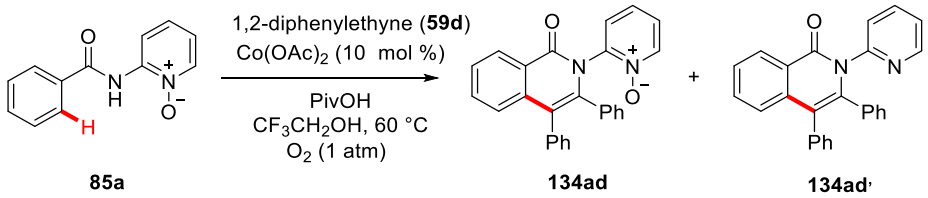


Figure S-1: O_2-uptake with terminal alkyne **59j**.

2) **O_2-uptake Study with Internal Alkyne 59d**



The general procedure **G** was followed, using aromatic amide **85a** (207 mg, 1.00 mmol), alkyne **59d** (214 mg, 1.20 mmol), PivOH (204 mg, 2.0 mmol) and $Co(OAc)_2$ (18 mg, 10 mol %). The Schlenk tube was connected to a burette with a reservoir filled with O_2-saturated water. The mixture was stirred at 60 ºC and the changes in volume were determined as shown in Table S-3. At ambient temperature, the reaction was stopped with saturated aqueous $NaHCO_3$ (30 mL). This mixture was extracted with CH_2Cl_2 (4×20 mL) and dried over Na_2SO_4. Evaporation of the solvents and purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1→CH_2Cl_2/acetone 2:1) yielded **134ad** (285 mg, 73%) and **134ad'** (65 mg, 17%) as colorless solids.

Table S-2: O_2-uptake Study.

t / h	V / mL	ΔV / mL	n / mmol
0	23.5	0	0
0.083	23.5	0	0
0.167	23.5	0	0
0.250	23.5	0	0
0.333	23.5	0	0
0.417	23.2	0.3	0.013
0.500	23.1	0.4	0.018
0.583	23.0	0.5	0.022
0.667	23.0	0.5	0.022
0.750	22.9	0.6	0.027
0.833	22.7	0.8	0.036
0.917	22.6	0.9	0.040
1.000	22.5	1.0	0.045
1.167	22.4	1.1	0.049
1.333	22.3	1.2	0.054
1.500	22.1	1.4	0.062
1.667	22.0	1.5	0.067
1.833	21.8	1.7	0.076
2.000	21.6	1.9	0.085
2.167	21.4	2.1	0.094
2.500	21.4	2.1	0.094
3.500	20.8	2.7	0.120
3.667	20.6	2.9	0.129
4.667	20.1	3.4	0.152
5.417	19.3	4.2	0.187
5.917	18.9	4.6	0.205
6.333	18.5	5.0	0.223
6.667	18.4	5.1	0.228
7.667	17.7	5.8	0.259
8.167	17.4	6.1	0.272
8.833	17.0	6.5	0.290
9.333	16.6	6.9	0.308
9.917	16.3	7.2	0.321
12.000	15.5	8.0	0.357
12.333	15.4	8.1	0.362
13.333	14.9	8.6	0.384
16.000	14.5	9	0.402

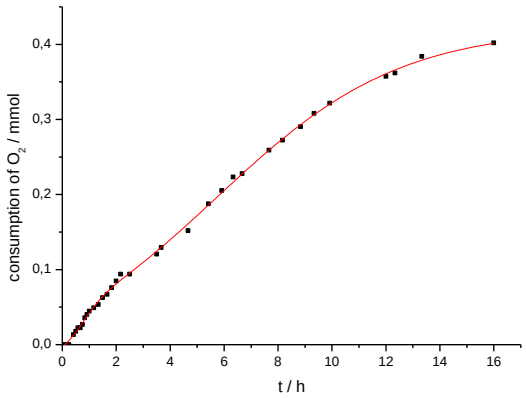
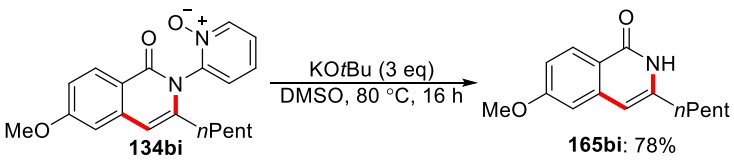


Figure S-2: O_2-uptake with internal alkyne **59d**.

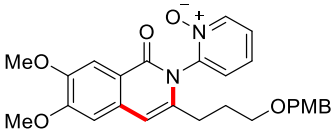
Removal of Directing Group



6-Methoxy-3-*n*-pentylisoquinolin-1(2*H*)-one (165bi): To a 25 mL Schlenk tube was added **134bi** (169 mg, 0.50 mmol), KO*t*Bu (168 mg, 1.50 mmol) and DMSO (5.0 mL) under an atmosphere of N_2. The reaction mixture was heated to 80 ºC for 16 h. At ambient temperature, the reaction mixture was diluted with EtOAc (100 mL) and washed with H_2O (30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4, evaporation of the solvents and purification by column chromatography on silica gel (*n*-hexane/EtOAc: 2:1→1:1) afforded **165bi** (96 mg, 78%) as a pale yellow solid.

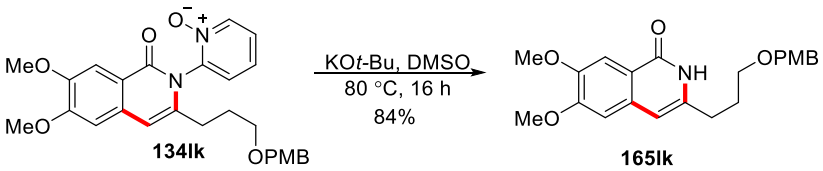
M. p. = 120–121 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 11.78 (s, 1H), 8.29 (d, J = 8.9 Hz, 1H), 6.99 (dd, J = 8.9, 2.5 Hz, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.23 (s, 1H), 3.88 (s, 3H), 2.63 (t, J = 7.6 Hz, 2H), 1.76 (m, 2H), 1.46–1.27 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 164.5 (C_q), 162.8 (C_q), 143.2 (C_q), 140.9 (C_q), 129.1 (CH), 118.2 (C_q), 115.3 (CH), 106.1 (CH), 103.5 (CH), 55.3 (CH_3), 33.3 (CH_2), 31.2 (CH_2), 28.0 (CH_2), 22.3 (CH_2), 13.9 (CH_3). **IR** (ATR): 2930, 1632, 1602, 1497, 1454, 1434, 1371, 1245, 1166, 863 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 246 (10) [M+H$^+$], 245 (40) [M$^+$], 202 (20), 189 (100), 161 (20), 146 (10). **HR-MS** (EI) *m/z* calcd for $C_{15}H_{19}NO_2$ [M$^+$], 245.1416, found 245.1417.

Synthesis of Di-Methoxyrosettacin 170



2-[6,7-Dimethoxy-3-(3-((4-methoxybenzyl)oxy)propyl)-1-oxoisoquinolin-2(1*H*)-yl] pyridine 1-oxide (134lk): The general procedure **G** was followed, by using amide **85l** (1.37 g, 5.0 mmol), alkyne **59k** (1.22 g, 6.0 mmol), PivOH (1.02 g, 10.0 mmol) and $Co(OAc)_2$ (88 mg, 10 mol %) in TFE (20 mL). Purification by column chromatography on silica gel (CH_2Cl_2/acetone 3:1) afforded the product **134lk** (1.69 g, 71%) as a colorless solid.

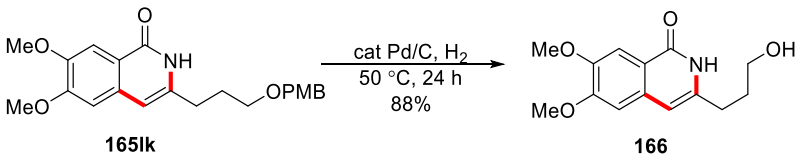
M. p. = 164–165 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.40–8.33 (m, 1H), 7.71 (s, 1H), 7.49–7.39 (m, 1H), 7.36–7.29 (m, 2H), 7.20–7.14 (m, 2H), 6.89–6.82 (m, 2H), 6.82 (s, 1H), 6.33 (s, 1H), 4.34 (s, 2H), 4.00 (s, 3H), 3.95 (s, 3H), 3.80 (s, 3H), 3.47–3.28 (m, 2H), 2.54–2.25 (m, 2H), 1.85–1.75 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ =161.9 (C_q), 159.1 (C_q), 154.1 (C_q), 148.8 (C_q), 144.6 (C_q), 140.6 (CH), 140.4 (C_q), 133.0 (C_q), 130.4 (C_q), 129.2 (CH), 128.0 (CH), 125.9 (CH), 125.3 (CH), 118.1 (C_q), 113.7 (CH), 108.1 (CH), 106.0 (CH), 104.9 (CH), 72.4 (CH_2), 68.4 (CH_2), 56.1 (CH_3), 56.1 (CH_3) 55.3 (CH_3), 28.7 (CH_2), 27.7 (CH_2). **IR** (ATR): 3048, 2945, 2857, 1664, 1596, 1248, 1160, 1031, 754 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 460 (20), 355 (10), 340 (20), 339 (70), 323 (35), 309 (40), 295 (60), 121 (100). **HR-MS** (ESI) *m/z* calcd for $C_{27}H_{29}N_2O_6$ [M+H$^+$], 477.2020, found 477.2018.



6, 7-Dimethoxy-3-[3-{(4-methoxybenzyl)oxy}propyl]isoquinolin-1(2*H*)-one (165lk): to a 100 mL Schlenk tube was added **134lk** (1.67 g, 3.50 mmol), KO*t*-Bu (1.18 g, 10.50 mmol) and DMSO (35 mL) under an atmosphere of N_2, the reaction mixture was heated to 80 ºC for 16 h. At ambient temperature, the reaction was diluted with EtOAc (200 mL) and washed with H_2O (40 mL) and brine (40 mL). The organic phase was dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography on silica gel (*n*-hexane/EtOAc: 2:1→1:1) afforded **165lk** (1.13 g, 84%) as a pale yellow solid.

M. p. = 136–137 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 10.10 (s, 1H), 7.72 (s, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.81 (s, 1H), 6.17 (s, 1H), 4.48 (s, 2H), 3.98 (s, 3H), 3.97 (s, 3H), 3.80 (s, 3H), 3.52 (t, *J* = 5.9 Hz, 2H), 2.69 (t, *J* = 7.2 Hz, 2H), 2.05–1.94 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 163.3 (C_q), 159.2 (C_q), 153.7 (C_q), 148.6 (C_q), 139.4 (C_q), 134.1 (C_q), 130.2 (C_q), 129.5 (CH), 118.3 (C_q), 113.8 (CH), 107.1 (CH), 105.8 (CH), 103.6 (CH), 72.7 (CH_2), 68.3 (CH_2), 56.1 (CH_3), 56.0 (CH_3), 55.2 (CH_3), 30.1 (CH_2),

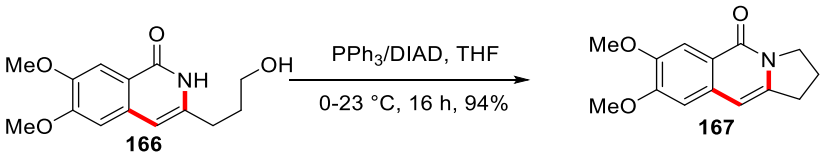
28.3 (CH_2). **IR** (ATR): 2935, 1636, 1608, 1498, 1395, 1249, 1219, 994, 825 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 384 (10) [M+H$^+$], 383 (40) [M$^+$], 339 (10), 262 (20), 247 (15), 232 (25), 219 (20), 121 (100).**HR-MS** (ESI) *m/z* calcd for $C_{22}H_{25}NO_5$ [M$^+$], 383.1733, found 383.1724.



165lk **166**

3-(3-Hydroxypropyl)-6, 7-dimethoxyisoquinolin-1(2*H*)-one (166): to a solution of ether **165lk** (958 mg, 2.5 mmol) in EtOH (20 mL) was added Pd/C (96 mg, 10 mol %). The reaction mixture was set under hydrogen atmosphere (1 atm H_2) and heated to 50 ºC for 24 h. The reaction mixture was filtered through Celite, and after removal of the solvent the crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH 10:1) to give **166** (579 mg, 88 %) as a colorless solid.

M. p. = 252–253 ºC. **^{1}H NMR** (300 MHz, DMSO-d_6) δ = 11.01 (s_{br}, 1H), 7.50 (s, 1H), 7.04 (s, 1H), 6.24 (s, 1H), 4.49 (s_{br}, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.44 (t, *J* = 6.6 Hz, 2H), 2.56–2.45 (m, 2H), 1.81–1.71 (m, 2H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ = 161.8 (C_q), 153.1 (C_q), 147.9 (C_q), 140.6 (C_q), 133.6 (C_q), 117.7 (C_q), 106.6 (CH), 106.3 (CH), 101.7 (CH), 59.8 (CH_2), 55.6 (CH_3), 55.4 (CH_3), 31.1 (CH_2), 28.8 (CH_2). **IR** (ATR): 3373, 2937, 1626, 1602, 1552, 1500, 1263, 1221, 877, 658 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 364 (20) [M+H$^+$], 363 (90) [M$^+$], 248 (10), 232 (20), 219 (100), 204 (30), 188 (10), 174 (10). **HR-MS** (EI) *m/z* calcd for $C_{14}H_{17}NO_4$ [M$^+$], 263.1158, found 263.1153.

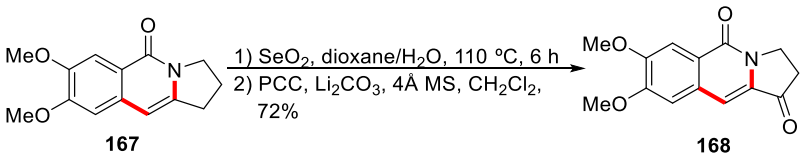


166 **167**

7, 8-Dimethoxy-2, 3-dihydropyrrolo [1, 2-b] isoquinolin-5(1*H*)-one (167):[134] a 50 mL flask was charged with compound **166** (527 mg, 2.0 mmol), PPh_3 (787 mg, 3.0 mmol), and THF (15 mL). Diisopropyl azodicarboxylate (0.6 mL, 3.0 mmol) in THF (5.0 mL) was added dropwise at 0 ºC. Upon completion of the addition, the mixture was allowed to warm to ambient temperature and was stirred for 16 h. The solvent was removed and the residue purified by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) to afford **167** (461 mg, 94%) as a colorless solid.

M. p. = 190–191 ºC. **^{1}H NMR** (300 MHz, DMSO-d_6) δ = 7.73 (s, 1H), 6.79 (s, 1H), 6.31 (s, 1H), 4.15 (t, *J* = 7.2 Hz, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 3.06 (t, *J* = 7.6 Hz, 2H), 2.22–2.12 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.7 (C_q), 153.0 (C_q), 148.2 (C_q), 142.2 (C_q), 133.5 (C_q), 118.3 (C_q), 107.0 (CH), 105.5 (CH), 99.7 (CH), 56.0 (CH_3), 55.8 (CH_3), 47.9 (CH_2), 31.0 (CH_2), 21.9 (CH_2). **IR** (ATR): 3055, 2891, 2824, 1660, 1596, 1506,

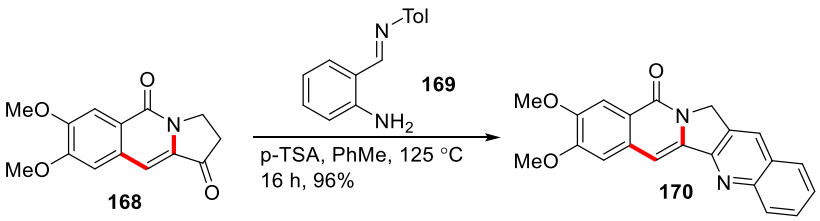
1454, 1252, 1119, 997 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 246 (20) [M+H^+], 245 (100) [M^+], 230 (75), 202 (40), 200 (25), 172(20), 159 (15). **HR-MS** (EI) *m/z* calcd for $C_{14}H_{15}NO_3$ [M^+], 245.1052, found 245.1058.



167 168

7, 8-Dimethoxy-2, 3-dihydropyrrolo [1, 2-b] isoquinoline-1, 5-dione (168):[134] a mixture of compound **167** (368 mg, 1.5 mmol) and SeO_2 (200 mg, 1.8 mmol) in 1,4-dioxane (15 mL) and H_2O (0.5 mL) was heated at 110 °C for 6 h. At ambient temperature, the reaction mixture was diluted with CH_2Cl_2(40 mL), filtered through Celite, and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL), Li_2CO_3 (222 mg, 3.0 mmol) and 4 Å molecular sieve (1.10 g) was added. PCC (647 mg, 3.0 mmol) was added in one portion at 0 ºC. The mixture was allowed to warm to ambient temperature and stirred for 24 h. The reaction mixture was then diluted with CH_2Cl_2(40 mL) and filtered through Celite. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) to give **168** (280 mg, 72%) as an off-white solid.

M. p. = 249–250 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.84 (s, 1H), 7.19 (s, 1H), 7.06 (s, 1H), 4.37 (t, *J* = 7.1 Hz, 2H), 4.05 (s, 3H), 4.02 (s, 3H), 2.93 (t, *J* = 7.1 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 197.6 (C_q), 160.3 (C_q), 153.5 (C_q), 151.5 (C_q), 133.4 (C_q), 131.2 (C_q), 123.1 (C_q), 108.4 (CH), 107.3 (CH), 104.7 (CH), 56.4 (CH_3), 56.2 (CH_3), 41.5 (CH_2), 34.1 (CH_2). **IR** (ATR): 3062, 2928, 2830, 1720, 1643, 1508, 1462, 1093, 653 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 260 (20) [M+H^+], 259 (100) [M^+], 244 (30), 214 (40), 188 (30), 160(35), 117 (20). **HR-MS** (EI) *m/z* calcd for $C_{14}H_{13}NO_4$ [M^+], 259.0845, found 259.0852.



168 170

8, 9-Dimethoxybenzo[6, 7]indolizino[1, 2-b] quinolin-11(13*H*)-one (170):[134] a mixture of ketone **168** (52 mg, 0.20 mmol), 2-aminobenzylidene-*p*-tolylamine (**169)** (46 mg, 0.22 mmol), and *p*-toluenesulfonic acid monohydrate (2.6 mg 0.014 mmol) in PhMe (2.0 mL) was stirred at 125 ºC for 16 h in a 20 mL sealed tube. Then, the reaction mixture was allowed to cool to ambient temperature. The solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/acetone 1:1) to give **170** (66 mg, 96%) as an off-white solid.

M. p. = 301–303 ºC. **^{1}H NMR** (300 MHz, DMSO-d_6, 120 ºC) δ = 8.55 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.07–8.02 (m, 1H), 7.85–7.80 (m, 1H), 7.79 (s, 1H), 7.65 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.55 (s, 1H), 7.43 (s, 1H),

5.31 (d, J = 1.3 Hz, 2H), 3.98 (s, 3H), 3.95 (s, 3H). **^{13}C NMR** (75 MHz, DMSO-d_6, 120 °C) δ = 158.6 (C_q), 153.1 (C_q), 153.0 (C_q), 149.3 (C_q), 147.7 (C_q), 138.4 (C_q), 132.2 (C_q), 130.2 (CH), 129.1 (CH), 128.8 (C_q), 128.2 (CH), 127.6 (CH), 127.2 (C_q), 126.2 (CH), 119.5 (C_q), 108.3 (CH), 107.5 (CH), 98.9 (CH), 55.5 (CH_3), 55.5 (CH_3), 48.7 (CH_2). **IR** (neat): 3059, 3006, 2924, 1651, 1597, 1504, 1446, 1272, 1023, 789 cm^{-1}. **MS** (EI) *m/z* (relative intensity) 345 (2) [M+H^+], 344 (15) [M^+], 329 (10), 301 (10), 229 (5), 121 (5), 84 (60), 66 (100). **HR-MS** (EI) *m/z* calcd for $C_{21}H_{16}N_2O_3$ [M^+], 344.1161, found 344.1157.

Reference

[1] (a) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417-1492; (b) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780-1824; (c) Shi, W.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2011**, *40*, 2761-2776; (d) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440-1449; (e) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461-1473; (f) Würtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523-1533; (g) Nicolaou, K.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489; (h) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337-2364; (i) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147-168; (j) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263-303; (k) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.

[2] (a) Santoro, S.; Ferlin, F.; Luciani, L.; Ackermann, L.; Vaccaro, L. *Green Chem.* **2017**, *19*, 1601-1612; (b) Borie, C.; Ackermann, L.; Nechab, M. *Chem. Soc. Rev.* **2016**, *45*, 1368-1386; (c) Ye, B.; Cramer, N. *Acc. Chem. Res.* **2015**, *48*, 1308-1318; (d) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040-1052; (e) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053-1064; (f) Ackermann, L. *Org. Process Res. Dev.* **2015**, *19*, 260-269; (g) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun.* **2014**, *50*, 29-39; (h) Mesganaw, T.; Ellman, J. A. *Org. Process Res. Dev.* **2014**, *18*, 1097-1104; (i) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443-1460; (j) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208-1219; (k) Ackermann, L. *J. Org. Chem.* **2014**, *79*, 8948-8954; (l) Ackermann, L. *Acc. Chem. Res.* **2013**, *47*, 281-295; (m) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215-1292; (n) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068-5083; (o) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242-3272; (p) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826; (q) Ackermann, L. *Synlett* **2007**, 507-526.

[3] (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315-1345; (b) Balcells, D.; Clot, E.; Eisenstein, O. *Chem. Rev.* **2010**, *110*, 749-823; (c) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5820-5831.

[4] Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118-1126.

[5] Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5887-5893.

[6] Oxgaard, J.; Tenn, W. J.; Nielsen, R. J.; Periana, R. A.; Goddard, W. A. *Organometallics* **2007**, *26*, 1565-1567.

[7] (a) Zell, D.; Bursch, M.; Müller, V.; Grimme, S.; Ackermann, L. *Angew. Chem. Int. Ed.*, n/a-n/a; (b) Mei, R.; Loup, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 793-797; (c) Ma, W.; Mei, R.; Tenti, G.; Ackermann, L. *Chem. – Eur. J.* **2014**, *20*, 15248-15251; (d) Wang, H.; Moselage, M.; González, M. J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 2705-2709.

[8] Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568-1576.

[9] Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936-946.

[10] (a) Bringmann, G.; Gulder, T.; Gulder, T. A.; Breuning, M. *Chem. Rev.* **2010**, *111*, 563-639; (b) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193-3207; (c) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem. Int. Ed.* **1990**, *29*, 977-991.

[11] (a) Mistry, N. B.; Westheim, A. S.; Kjeldsen, S. E. *Exp. Opin. Pharmacother.* **2006**, *7*, 575-581; (b) Matheron, M.; Porchas, M. *Plant Dis.* **2004**, *88*, 665-668; (c) Julius, S.; Kjeldsen, S. E.; Weber, M.; Brunner, H. R.; Ekman, S.; Hansson, L.; Hua, T.; Laragh, J.; McInnes, G. T.; Mitchell, L. *Lancet* **2004**, *363*, 2022-2031; (d) Cohn, J. N.; Tognoni, G. *N. Engl. J. Med.* **2001**, *345*, 1667-1675; (e) Brenner, B. M.; Cooper, M. E.; de Zeeuw, D.; Keane, W. F.; Mitch, W. E.; Parving, H.-H.; Remuzzi, G.; Snapinn, S. M.; Zhang, Z.; Shahinfar, S. *N. Engl. J. Med.* **2001**, *345*, 861-869.

[12] Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263-303.

[13] (a) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826; (b) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949-957.

[14] Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698-1699.
[15] Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936-5945.
[16] (a) Dastbaravardeh, N.; Schnürch, M.; Mihovilovic, M. D. *Org. Lett.* **2012**, *14*, 1930-1933; (b) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220-14221.
[17] (a) Kitazawa, K.; Kochi, T.; Sato, M.; Kakiuchi, F. *Org. Lett.* **2009**, *11*, 1951-1954; (b) Nakazono, S.; Easwaramoorthi, S.; Kim, D.; Shinokubo, H.; Osuka, A. *Org. Lett.* **2009**, *11*, 5426-5429.
[18] (a) Chinnagolla, R. K.; Vijeta, A.; Jeganmohan, M. *Chem. Commun.* **2015**, *51*, 12992-12995; (b) Hubrich, J.; Himmler, T.; Rodefeld, L.; Ackermann, L. *Adv. Synth. Catal.* **2015**, *357*, 474-480; (c) Sollert, C.; Devaraj, K.; Orthaber, A.; Gates, P. J.; Pilarski, L. T. *Chem. – Eur. J.* **2015**, *21*, 5380-5386; (d) Chinnagolla, R. K.; Jeganmohan, M. *Chem. Commun.* **2014**, *50*, 2442-2444; (e) Chinnagolla, R. K.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 5246-5249.
[19] Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579-2581.
[20] (a) Lakshman, M. K.; Deb, A. C.; Chamala, R. R.; Pradhan, P.; Pratap, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 11400-11404; (b) Oi, S.; Sasamoto, H.; Funayama, R.; Inoue, Y. *Chem. Lett.* **2008**, *37*, 994-995; (c) Oi, S.; Funayama, R.; Hattori, T.; Inoue, Y. *Tetrahedron* **2008**, *64*, 6051-6059; (d) Oi, S.; Sakai, K.; Inoue, Y. *Org. Lett.* **2005**, *7*, 4009-4011; (e) Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113-3119; (f) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783-1785.
[21] Ouellet, S. G.; Roy, A. l.; Molinaro, C.; Angelaud, R. m.; Marcoux, J.-F. o.; O'Shea, P. D.; Davies, I. W. *J. Org. Chem.* **2011**, *76*, 1436-1439.
[22] Bedford, R. B.; Cazin, C. S.; Holder, D. *Coord. Chem. Rev.* **2004**, *248*, 2283-2321.
[23] Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4176-4211.
[24] Ackermann, L. *Org. Lett.* **2005**, *7*, 3123-3125.
[25] Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 2619-2622.
[26] Ackermann, L.; Mulzer, M. *Org. Lett.* **2008**, *10*, 5043-5045.
[27] Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299-2302.
[28] Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032-5035.
[29] (a) Hubrich, J.; Ackermann, L. *Eur. J. Org. Chem.* **2016**, 3700-3704; (b) Hubrich, J.; Himmler, T.; Rodefeld, L.; Ackermann, L. *ACS Catal.* **2015**, *5*, 4089-4093; (c) Ackermann, L.; Pospech, J.; Potukuchi, H. K. *Org. Lett.* **2012**, *14*, 2146-2149; (d) Ackermann, L.; Diers, E.; Manvar, A. *Org. Lett.* **2012**, *14*, 1154-1157.
[30] (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2014**, *114*, 1783-1826; (b) Alabugin, I. V.; Gold, B. *J. Org. Chem.* **2013**, *78*, 7777-7784; (c) Palisse, A.; Kirsch, S. F. *Org. Biomol. Chem.* **2012**, *10*, 8041-8047.
[31] (a) Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165-4179; (b) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2010**, *49*, 2096-2098.
[32] Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46-49.
[33] Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem.* **2010**, *2010*, 6495-6516.
[34] Kobayashi, K.; Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2002**, *124*, 8528-8529.
[35] Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742-7743.
[36] Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286-5287.
[37] Gu, Y.; Wang, X.-m. *Tetrahedron Lett.* **2009**, *50*, 763-766.
[38] Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250-3252.
[39] (a) Ye, X.; Xu, C.; Wojtas, L.; Akhmedov, N. G.; Chen, H.; Shi, X. *Org. Lett.* **2016**, *18*, 2970-2973; (b) He, J.; Wasa, M.; Chan, K. S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387-3390; (c) Ano, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2011**, *14*, 354-357; (d) Kim, S. H.; Yoon, J.; Chang, S. *Org. Lett.* **2011**, *13*, 1474-1477.
[40] (a) Ruan, Z.; Lackner, S.; Ackermann, L. *ACS Catal.* **2016**, *6*, 4690-4693; (b) Punji, B.; Khake, S. M.; Soni, V.; Gonnade, R. G. *Chem. – Eur. J.* **2016**; (c) Liu, Y.-H.; Liu, Y.-J.; Yan, S.-Y.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 11650-11653; (d) Yi, J.; Yang, L.; Xia, C.; Li, F. *J. Org. Chem.* **2015**, *80*, 6213-6221; (e) Matsuyama, N.; Kitahara, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2358-2361; (f) Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 4156-4159.

[41] (a) Shaikh, A. C.; Shinde, D. R.; Patil, N. T. *Org. Lett.* **2016**, *18*, 1056-1059; (b) Li, Y.; Xie, F.; Li, X. *J. Org. Chem.* **2016**, *81*, 715-722; (c) Finkbeiner, P.; Kloeckner, U.; Nachtsheim, B. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 4949-4952; (d) Jin, N.; Pan, C.; Zhang, H.; Xu, P.; Cheng, Y.; Zhu, C. *Adv. Synth. Catal.* **2015**, *357*, 1149-1153; (e) Collins, K. D.; Lied, F.; Glorius, F. *Chem. Commun.* **2014**, *50*, 4459-4461; (f) Feng, C.; Loh, T.-P. *Angew. Chem. Int. Ed.* **2014**, *53*, 2722-2726; (g) Feng, C.; Feng, D.; Loh, T.-P. *Chem. Commun.* **2014**, *50*, 9865-9868.

[42] (a) Tang, G.-D.; Pan, C.-L.; Xie, F. *Org. Biomol. Chem.* **2016**, *14*, 2898-2904; (b) Wu, Y.; Yang, Y.; Zhou, B.; Li, Y. *J. Org. Chem.* **2015**, *80*, 1946-1951.

[43] (a) Boobalan, R.; Gandeepan, P.; Cheng, C.-H. *Org. Lett.* **2016**, *18*, 3314-3317; (b) Mei, R.; Zhu, C.; Ackermann, L. *Chem. Commun.* **2016**, *52*, 13171-13174; (c) Zhang, L.; Chen, C.; Han, J.; Huang, Z.-B.; Zhao, Y. *Org. Chem. Front.* **2016**, *3*, 1271-1275; (d) Ano, Y.; Tobisu, M.; Chatani, N. *Synlett* **2012**, *23*, 2763-2767.

[44] Shang, M.; Wang, H.-L.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 11590-11593.

[45] Sauermann, N.; Gonzalez, M. J.; Ackermann, L. *Org. Lett.* **2015**, *17*, 5316-5319.

[46] Ruan, Z.; Sauermann, N.; Manoni, E.; Ackermann, L. *Angew. Chem.* **2017**, *129*, 3220-3224.

[47] Cera, G.; Haven, T.; Ackermann, L. *Chem. – Eur. J.* **2017**, *23*, 3577-3582.

[48] Li, Y.; Hari, D. P.; Vita, M. V.; Waser, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 4436-4454.

[49] (a) Xue, X.-S.; Ji, P.; Zhou, B.; Cheng, J.-P. *Chem. Rev.* **2017**, *117*, 8622-8648; (b) Wei, Y.; Hu, P.; Zhang, M.; Su, W. *Chem. Rev.* **2017**, *13*, 8864–8907; (c) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. *Chem. Rev.* **2017**, *117*, 8908-8976; (d) Wang, F.; Yu, S.; Li, X. *Chem. Soc. Rev.* **2016**, *45*, 6462-6477.

[50] (a) Ackermann, L.; Li, J. *Nat. Chem.* **2015**, *7*, 686-687; (b) Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Chem. Sci.* **2014**, *5*, 2146-2159; (c) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res* **2012**, *45*, 788-802; (d) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879-5918; (e) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2011**, *45*, 814-825; (f) Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2011**, *45*, 826-839.

[51] (a) Su, B.; Cao, Z.-C.; Shi, Z.-J. *Acc. Chem. Res.* **2015**, *48*, 886-896; (b) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, *2013*, 19-30; (c) Yoshikai, N. *Synlett* **2011**, 1047-1051; (d) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061-6067.

[52] (a) Hebrard, F.; Kalck, P. *Chem. Rev.* **2009**, *109*, 4272-4282; (b) Kharasch, M.; Fields, E. *J. Am. Chem. Soc.* **1941**, *63*, 2316-2320.

[53] (a) Wei, D.; Zhu, X.; Niu, J. L.; Song, M. P. *ChemCatChem* **2016**, *8*, 1242-1263; (b) Yoshikai, N. *ChemCatChem* **2015**, *7*, 732-734; (c) Moselage, M.; Li, J.; Ackermann, L. *ACS Catal.* **2015**, *6*, 498-525; (d) Yoshikai, N. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 843-857; (e) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208-1219; (f) Ackermann, L. *J. Org. Chem.* **2014**, *79*, 8948-8954; (g) Yoshikai, N. *Synlett* **2011**, 1047-1051.

[54] Klein, H.-F.; Helwig, M.; Koch, U.; Flörke, U.; Haupt, H.-J. *Z. Naturforsch. B Chem. Sci.* **1993**, *48*, 778-784.

[55] (a) Klein, H.-F.; Beck, R.; Flörke, U.; Haupt, H.-J. *Eur. J. Inorg. Chem.* **2003**, *2003*, 1380-1387; (b) Klein, H.-F.; Schneider, S.; He, M.; Floerke, U.; Haupt, H.-J. *Eur. J. Inorg. Chem.* **2000**, *2000*, 2295-2301.

[56] Klein, H.-F.; Camadanli, S.; Beck, R.; Leukel, D.; Flörke, U. *Angew. Chem. Int. Ed.* **2005**, *44*, 975-977.

[57] Camadanli, S.; Beck, R.; Flörke, U.; Klein, H.-F. *Dalton Trans.* **2008**, 5701-5704.

[58] Beck, R.; Sun, H.; Li, X.; Camadanli, S.; Klein, H. F. *Eur. J. Inorg. Chem.* **2008**, 3253-3257.

[59] (a) Murahashi, S.; Horiie, S. *J. Am. Chem. Soc.* **1956**, *78*, 4816-4817; (b) Murahashi, S. *J. Am. Chem. Soc.* **1955**, *77*, 6403-6404.

[60] Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *133*, 428-429.

[61] (a) Sauermann, N.; Loup, J.; Kootz, D.; Yatham, V. R.; Berkessel, A.; Ackermann, L. *Synthesis* **2017**, *149*, 3476-3484; (b) Song, W.; Ackermann, L. *Angew. Chem.* **2012**, *124*, 8376-8379; (c) Punji, B.;

Song, W.; Shevchenko, G. A.; Ackermann, L. *Chem. – Eur. J.* **2013**, *19*, 10605-10610; (d) Li, J.; Ackermann, L. *Chem. – Eur. J.* **2015**, *21*, 5718-5722.
[62] Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249-12251.
[63] Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 17283-17295.
[64] (a) Ding, Z.; Yoshikai, N. *Org. Lett.* **2010**, *12*, 4180-4183; (b) Ding, Z.; Yoshikai, N. *Angew. Chem.* **2012**, *124*, 4776-4779.
[65] Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *133*, 400-402.
[66] Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 9279-9282.
[67] (a) Song, W.; Ackermann, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 8251-8254; (b) Punji, B.; Song, W.; Shevchenko, G. A.; Ackermann, L. *Chem. – Eur. J.* **2013**, *19*, 10605-10610.
[68] Gao, K.; Lee, P.-S.; Long, C.; Yoshikai, N. *Org. Lett.* **2012**, *14*, 4234-4237.
[69] Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154-13155.
[70] (a) Castro, L. C. M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 410-421; (b) Yokota, A.; Aihara, Y.; Chatani, N. *J. Org. Chem.* **2014**, *79*, 11922-11932; (c) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898-901; (d) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726-11743; (e) Corbet, M.; De Campo, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 9896-9898; (f) Aihara, Y.; Chatani, N. *Chem. Sci.* **2013**, *4*, 664-670.
[71] Grigorjeva, L.; Daugulis, O. *Angew. Chem.* **2014**, *126*, 10373-10376.
[72] Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2014**, *16*, 4684-4687.
[73] Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2014**, *16*, 4688-4690.
[74] Kalsi, D.; Sundararaju, B. *Org. Lett.* **2015**, *17*, 6118-6121.
[75] Ma, W.; Ackermann, L. *ACS Catal.* **2015**, *5*, 2822-2825.
[76] Hao, X.-Q.; Chen, L.-J.; Ren, B.; Li, L.-Y.; Yang, X.-Y.; Gong, J.-F.; Niu, J.-L.; Song, M.-P. *Org. Lett.* **2014**, *16*, 1104-1107.
[77] Zhang, L. B.; Hao, X. Q.; Zhang, S. K.; Liu, Z. J.; Zheng, X. X.; Gong, J. F.; Niu, J. L.; Song, M. P. *Angew. Chem. Int. Ed.* **2015**, *54*, 272-275.
[78] (a) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651-3678; (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2009**, *110*, 624-655.
[79] (a) Nakamura, E.; Hatakeyama, T.; Ito, S.; Ishizuka, K.; Ilies, L.; Nakamura, M. *Organic Reactions* **2014**; (b) Nakao, Y. *Chem. Rec.* **2011**, *11*, 242-251; (c) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, *2009*, 4087-4109.
[80] (a) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 2207-2211; (b) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Chem. – Eur. J.* **2013**, *19*, 9142-9146.
[81] Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M. *J. Am. Chem. Soc.* **2014**, *136*, 5424-5431.
[82] Li, W.; Weng, L.-H.; Jin, G.-X. *Inorg. Chem. Commun.* **2004**, *7*, 1174-1177.
[83] Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Adv. Synth. Catal.* **2014**, *356*, 1491-1495.
[84] Hummel, J. R.; Ellman, J. A. *J. Am. Chem. Soc.* **2015**, *137*, 490-498.
[85] Li, J.; Ackermann, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 3635-3638.
[86] Yu, D.-G.; Gensch, T.; de Azambuja, F.; Vásquez-Céspedes, S.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17722-17725.
[87] (a) Moselage, M.; Sauermann, N.; Koeller, J.; Liu, W.; Gelman, D.; Ackermann, L. *Synlett* **2015**, *26*, 1596-1600; (b) Pawar, A. B.; Chang, S. *Org. Lett.* **2015**, *17*, 660-663; (c) Yu, D.-G.; Gensch, T.; de Azambuja, F.; Vásquez-Céspedes, S.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17722-17725.
[88] Li, J.; Ackermann, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 8551-8554.
[89] (a) Intrieri, D.; Zardi, P.; Caselli, A.; Gallo, E. *Chem. Commun.* **2014**, *50*, 11440-11453; (b) Curtius, T. *Berichte der deutschen chemischen Gesellschaft* **1890**, *23*, 3023-3033.
[90] Hummel, J. R.; Ellman, J. A. *Org. Lett.* **2015**, *17*, 2400-2403.
[91] (a) Bentley, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444-463; (b) Bentley, K. W. *Nat. Prod. Rep.* **2004**, *21*, 395-424.

[92] Wang, H.; Koeller, J.; Liu, W.; Ackermann, L. *Chem. – Eur. J.* **2015**, *21*, 15525-15528.
[93] Sun, B.; Yoshino, T.; Kanai, M.; Matsunaga, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 12968-12972.
[94] Sen, M.; Kalsi, D.; Sundararaju, B. *Chem. – Eur. J.* **2015**, *21*, 15529-15533.
[95] (a) Kornhaaß, C.; Kuper, C.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1619-1624; (b) Kornhaaß, C.; Li, J.; Ackermann, L. *J. Org. Chem.* **2012**, *77*, 9190-9198; (c) Zhang, X.; Chen, D.; Zhao, M.; Zhao, J.; Jia, A.; Li, X. *Adv. Synth. Catal.* **2011**, *353*, 719-723; (d) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688-5691; (e) Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 572-577.
[96] Ackermann, L., *Modern Arylation Methods*. John Wiley & Sons: 2009.
[97] Zhang, F.; Spring, D. R. *Chem. Soc. Rev.* **2014**, *43*, 6906-6919.
[98] (a) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461-1479; (b) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788-802.
[99] (a) Schrittwieser, J. H.; Resch, V.; Sattler, J. H.; Lienhart, W. D.; Durchschein, K.; Winkler, A.; Gruber, K.; Macheroux, P.; Kroutil, W. *Angew. Chem. Int. Ed.* **2011**, *50*, 1068-1071; (b) Chen, D. Y.-K.; Youn, S. W. *Chem. – Eur. J.* **2012**, *18*, 9452-9474; (c) Chen, D. Y. K.; Youn, S. W. *Chem. – Eur. J.* **2012**, *18*, 9452-9474; (d) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960-9009; (e) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885-1898; (f) O'Malley, S. J.; Tan, K. L.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13496-13497; (g) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824.
[100] Wang, L.; Ackermann, L. *Org. Lett.* **2012**, *15*, 176-179.
[101] (a) Tangdenpaisal, K.; Worayuthakarn, R.; Karnkla, S.; Ploypradith, P.; Intachote, P.; Sengsai, S.; Saimanee, B.; Ruchirawat, S.; Chittchang, M. *Chem. Asian J.* **2015**, *10*, 925-937; (b) Ballot, C.; Martoriati, A.; Jendoubi, M.; Buche, S.; Formstecher, P.; Mortier, L.; Kluza, J.; Marchetti, P. *Mar. Drugs* **2014**, *12*, 779-798; (c) Ballot, C.; Kluza, J.; Lancel, S.; Martoriati, A.; Hassoun, S. M.; Mortier, L.; Vienne, J.-C.; Briand, G.; Formstecher, P.; Bailly, C. *Apoptosis* **2010**, *15*, 769-781; (d) Baunbæk, D.; Trinkler, N.; Ferandin, Y.; Lozach, O.; Ploypradith, P.; Rucirawat, S.; Ishibashi, F.; Iwao, M.; Meijer, L. *Mar. Drugs* **2008**, *6*, 514-527; (e) Gallego, M.; Ballot, C.; Kluza, J.; Hajji, N.; Martoriati, A.; Castera, L.; Cuevas, C.; Formstecher, P.; Joseph, B.; Kroemer, G. *Oncogene* **2008**, *27*, 1981-1992; (f) Kluza, J.; Gallego, M.-A.; Loyens, A.; Beauvillain, J.-C.; Sousa-Faro, J.-M. F.; Cuevas, C.; Marchetti, P.; Bailly, C. *Cancer Res.* **2006**, *66*, 3177-3187; (g) Lambert, J. M. *Curr. Opin. Pharmacol.* **2005**, *5*, 543-549; (h) Facompré, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. *Cancer Res.* **2003**, *63*, 7392-7399; (i) Bailly, C. *Anticancer Agents Med. Chem.* **2004**, *4*, 363-378.
[102] Gao, K.; Yoshikai, N. *Chem. Commun.* **2012**, *48*, 4305-4307.
[103] (a) Mei, R.; Loup, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 793-797; (b) Li, B.; Devaraj, K.; Darcel, C.; Dixneuf, P. H. *Tetrahedron* **2012**, *68*, 5179-5184.
[104] (a) Li, Y.; Li, C.; Zheng, Y.; Wei, X.; Ma, Q.; Wei, P.; Liu, Y.; Qin, Y.; Yang, N.; Sun, Y.; Ling, Y.; Yang, X.; Wang, Q. *J. Agric. Food Chem.* **2014**, *62*, 3064-3072; (b) Mukai, A.; Fukai, T.; Matsumoto, Y.; Ishikawa, J.; Hoshino, Y.; Yazawa, K.; Harada, K.-i.; Mikami, Y. *J Antibiot* **2006**, *59*, 366-369.
[105] (a) Perrone, S.; Pilati, T.; Rosato, F.; Salomone, A.; Videtta, V.; Troisi, L. *Tetrahedron* **2011**, *67*, 2090-2095; (b) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297-2360; (c) Levin, J. I.; Weinreb, S. M. *Tetrahedron Lett.* **1982**, *23*, 2347-2350; (d) Bernardi, A.; Ouellet, S. G.; Angelaud, R.; O'Shea, P. D. *Tetrahedron Lett.* **2008**, *49*, 6707-6708; (e) Suresh Babu, M.; Lokanatha Rai, K. M. *Tetrahedron Lett.* **2004**, *45*, 7969-7970.
[106] (a) Li, Q.; Woods, K. W.; Claiborne, A.; Gwaltney, S. L.; Barr, K. J.; Liu, G.; Gehrke, L.; Credo, R. B.; Hui, Y. H.; Lee, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 465-469; (b) Mukai, A.; Fukai, T.; Matsumoto, Y.; Ishikawa, J.; Hoshino, Y.; Yazawa, K.; Harada, K.-i.; Mikami, Y. *J. Antibiot.* **2006**, *59*, 366.

[107] (a) Maiden, T. M.; Swanson, S.; Procopiou, P. A.; Harrity, J. *Chem. – Eur. J.* **2015**, *21*, 14342-14346; (b) Patel, P.; Chang, S. *Org. Lett.* **2014**, *16*, 3328-3331; (c) Lee, D.; Kim, Y.; Chang, S. *J. Org. Chem.* **2013**, *78*, 11102-11109; (d) Zhao, H.; Shang, Y.; Su, W. *Org. Lett.* **2013**, *15*, 5106-5109.

[108] Ma, W.; Ackermann, L. *ACS Catal.* **2015**, *5*, 2822-2825.

[109] Zhang, L. B.; Hao, X. Q.; Liu, Z. J.; Zheng, X. X.; Zhang, S. K.; Niu, J. L.; Song, M. P. *Angew. Chem. Int. Ed.* **2015**, *54*, 10012-10015.

[110] (a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788-802; (b) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461-1479.

[111] (a) Zhu, C.; Zhang, Y. K., Jian; Zhao, H.; Su, W. *Org. Lett.* **2015**, *17*, 3418-3421; (b) Huang, L.; Hackenberger, D.; Gooßen, L. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 12607-12611; (c) Arroniz, C.; Ironmonger, A.; Rassias, G.; Larrosa, I. *Org. Lett.* **2013**, *15*, 910-913; (d) Wu, Z.; Chen, S.; Hu, C.; Li, Z.; Xiang, H.; Zhou, X. *ChemCatChem* **2013**, *5*, 2839-2842; (e) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510-3511; (f) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879-9884.

[112] (a) Font, M.; Quibell, J. M.; Perry, G. J. P.; Larrosa, I. *Chem. Commun.* **2017**, *53*, 5584-5597; (b) Simonetti, M.; Larrosa, I. *Nat. Chem.* **2016**, *8*, 1086-1088; (c) Biafora, A.; Gooßen, L. J. *Synlett* **2017**, DOI: 10.1055/s-0036-1588450.

[113] Ackermann, L.; Born, R.; Vicente, R. *ChemSusChem* **2009**, *2*, 546-549.

[114] Warratz, S.; Kornhaaß, C.; Cajaraville, A.; Niepötter, B.; Stalke, D.; Ackermann, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 5513-5517.

[115] Biafora, A.; Krause, T.; Hackenberger, D.; Belitz, F.; Gooßen, L. J. *Angew. Chem.* **2016**, *128*, 14972-14975.

[116] (a) Seki, M. *Org. Process Res. Dev.* **2016**, *20*, 867-877; (b) Hubrich, J.; Himmler, T.; Rodefeld, L.; Ackermann, L. *ACS Catal.* **2015**, *5*, 4089-4093; (c) Lu, W.; Kuwabara, J.; Kanbara, T. *Macromol. Rapid Commun.* **2013**, *34*, 1151-1156.

[117] Biafora, A.; Gooßen, L. J. *Synlett*, DOI: 10.1055/s-0036-1588450.

[118] Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952-3015.

[119] Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264.

[120] Andersen, R. J.; Faulkner, D. J.; He, C. H.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1985**, *107*, 5492-5495.

[121] (a) Pla, D.; Albericio, F.; Alvarez, M. *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 746-760; (b) Pla, D.; Albericio, F.; Álvarez, M. *Med. Chem. Commun.* **2011**, *2*, 689-697.

[122] (a) Lade, D. M.; Pawar, A. B.; Mainkar, P. S.; Chandrasekhar, S. *J. Org. Chem.* **2017**, *82*, 4998-5004; (b) Manjappa, K. B.; Syu, J.-R.; Yang, D.-Y. *Org. Lett.* **2016**, *18*, 332-335; (c) Dialer, C.; Imbri, D.; Hansen, S. P.; Opatz, T. *J. Org. Chem.* **2015**, *80*, 11605-11610; (d) Ueda, K.; Amaike, K.; Maceiczyk, R. M.; Itami, K.; Yamaguchi, J. *J. Am. Chem. Soc.* **2014**, *136*, 13226-13232; (e) Komatsubara, M.; Umeki, T.; Fukuda, T.; Iwao, M. *J. Org. Chem.* **2013**, *79*, 529-537; (f) Li, Q.; Jiang, J.; Fan, A.; Cui, Y.; Jia, Y. *Org. Lett.* **2010**, *13*, 312-315; (g) Chen, L.; Xu, M. H. *Adv. Synth. Catal.* **2009**, *351*, 2005-2012; (h) Liermann, J. C.; Opatz, T. *J. Org. Chem.* **2008**, *73*, 4526-4531; (i) Fujikawa, N.; Ohta, T.; Yamaguchi, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *Tetrahedron* **2006**, *62*, 594-604; (j) Ploypradith, P.; Petchmanee, T.; Sahakitpichan, P.; Litvinas, N. D.; Ruchirawat, S. *J. Org. Chem.* **2006**, *71*, 9440-9448; (k) Pla Queral, D.; Marchal, A.; Olsen, C. A.; Francesch, A.; Cuevas, C.; Albericio Palomera, F.; Álvarez Domingo, M. *J. Med. Chem.* **2006**; (l) Pla, D.; Marchal, A.; Olsen, C. A.; Albericio, F.; Álvarez, M. *J. Org. Chem.* **2005**, *70*, 8231-8234; (m) Handy, S. T.; Zhang, Y.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362-2366; (n) Peschko, C.; Winklhofer, C.; Steglich, W. *Chem. – Eur. J.* **2000**, *6*, 1147-1152; (o) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54-62; (p) Banwell, M.; Hockless, D. *Chem. Commun.* **1997**, 2259-2260; (q) Heim, A.; Terpin, A.; Steglich, W. *Angew. Chem. Int. Ed.* **1997**, *36*, 155-156.

[123] (a) Handy, S. T.; Zhang, Y. *Org. Prep. Proc. Int.* **2005**, *37*, 411-445; (b) Imbri, D.; Tauber, J.; Opatz, T. *Mar. Drugs* **2014**, *12*, 6142-6177.

[124] (a) Yu, W.; Zhang, W.; Liu, Y.; Zhou, Y.; Liu, Z.; Zhang, Y. *RSC Adv.* **2016**, *6*, 24768-24772; (b) Lade, D. M.; Pawar, A. B. *Org. Chem. Front.* **2016**, *3*, 836-840; (c) Zhao, M.-N.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2014**, *16*, 608-611; (d) Xu, Y.-H.; He, T.; Zhang, Q.-C.; Loh, T.-P. *Chem. Commun.* **2014**, *50*, 2784-2786; (e) Hoshino, Y.; Shibata, Y.; Tanaka, K. *Adv. Synth. Catal.* **2014**, *356*, 1577-1585; (f) Li, B.; Wang, N.; Liang, Y.; Xu, S.; Wang, B. *Org. Lett.* **2012**, *15*, 136-139; (g) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326-18339; (h) Crawley, M. L.; Goljer, I.; Jenkins, D. J.; Mehlmann, J. F.; Nogle, L.; Dooley, R.; Mahaney, P. E. *Org. Lett.* **2006**, *8*, 5837-5840.

[125] Moselage, M.; Sauermann, N.; Richter, S. C.; Ackermann, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 6352-6355.

[126] (a) Hargaden, G. C.; Guiry, P. J. *Chem. Rev.* **2009**, *109*, 2505-2550; (b) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561-3651; (c) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151-4202.

[127] (a) Ma, W.; Gandeepan, P.; Li, J.; Ackermann, L. *Org. Chem. Front.* **2017**, *4*, 1435-1467; (b) Rousseau, G.; Breit, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 2450-2494.

[128] Gant, T. G.; Meyers, A. *Tetrahedron* **1994**, *50*, 2297-2360.

[129] (a) Bizet, V.; Bolm, C. *Eur. J. Org. Chem.* **2015**, *2015*, 2854-2860; (b) Park, Y.; Jee, S.; Kim, J. G.; Chang, S. *Org. Process Res. Dev.* **2015**, *19*, 1024-1029; (c) Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4534-4542; (d) Zhong, C. L.; Tang, B. Y.; Yin, P.; Chen, Y.; He, L. *J. Org. Chem.* **2012**, *77*, 4271-4277; (e) Middleton, W. J. *J. Org. Chem.* **1983**, *48*, 3845-3847.

[130] Sun, S.-Z.; Shang, M.; Wang, H.-L.; Lin, H.-X.; Dai, H.-X.; Yu, J.-Q. *J. Org. Chem.* **2015**, *80*, 8843-8848.

[131] (a) Liang, Y.; Liang, Y. F.; Tang, C.; Yuan, Y.; Jiao, N. *Chem. – Eur. J.* **2015**, *21*, 16395-16399; (b) Park, J.; Chang, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 14103-14107.

[132] (a) Bechtoldt, A.; Tirler, C.; Raghuvanshi, K.; Warratz, S.; Kornhaaß, C.; Ackermann, L. *Angew. Chem. Int. Ed.* **2016**, *55*, 264-267; (b) Warratz, S.; Kornhaaß, C.; Cajaraville, A.; Niepötter, B.; Stalke, D.; Ackermann, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 5513-5517; (c) Gligorich, K. M.; Sigman, M. S. *Chem. Commun.* **2009**, 3854-3867; (d) Wang, A.; Jiang, H.; Chen, H. *J. Am. Chem. Soc.* **2009**, *131*, 3846-3847.

[133] (a) Pin, F.; Comesse, S.; Sanselme, M.; Daïch, A. *J. Org. Chem.* **2008**, *73*, 1975-1978; (b) Cheng, K.; Rahier, N. J.; Eisenhauer, B. M.; Gao, R.; Thomas, S.; Hecht, S. M. *J. Am. Chem. Soc.* **2005**, *127*, 838-839; (c) Fox, B. M.; Xiao, X.; Antony, S.; Kohlhagen, G.; Pommier, Y.; Staker, B. L.; Stewart, L.; Cushman, M. *J. Med. Chem.* **2003**, *46*, 3275-3282.

[134] Xu, X.; Liu, Y.; Park, C. M. *Angew. Chem.* **2012**, *124*, 9506-9510.

[135] Demonceau, A.; Stumpf, A. W.; Saive, E.; Noels, A. F. *Macromolecules* **1997**, *30*, 3127-3136.

[136] Frei, R.; Waser, J. *J. Am. Chem. Soc.* **2013**, *135*, 9620-9623.

[137] Crestey, F.; Collot, V.; Stiebing, S.; Rault, S. *Synthesis* **2006**, *2006*, 3506-3514.

[138] Ishihara, M.; Togo, H. *Tetrahedron* **2007**, *63*, 1474-1480.

[139] (a) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc* **2013**, *135*, 9279-9282; (b) Herrmann, W. A.; Goossen, L. J.; Köcher, C.; Artus, G. R. *Angew. Chem. Int. Ed.* **1996**, *35*, 2805-2807; (c) Herrmann, W. A.; Köcher, C.; Gooßen, L. J.; Artus, G. R. *Chem. – Eur. J.* **1996**, *2*, 1627-1636.

[140] Bizet, V.; Buglioni, L.; Bolm, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 5639-5642.

[141] Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Chem. Commun.* **2015**, *51*, 4659-4661.

[142] Zhang, L. B.; Hao, X. Q.; Zhang, S. K.; Liu, Z. J.; Zheng, X. X.; Gong, J. F.; Niu, J. L.; Song, M. P. *Angew. Chem.* **2015**, *127*, 274-277.

[143] Chen, F.-J.; Liao, G.; Li, X.; Wu, J.; Shi, B.-F. *Org. Lett.* **2014**, *16*, 5644-5647.

[144] Pünner, F.; Schieven, J.; Hilt, G. *Org. Lett.* **2013**, *15*, 4888-4891.

[145] Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 3024-3033.

[146] Liu, Y.; Yang, Y.; Shi, Y.; Wang, X.; Zhang, L.; Cheng, Y.; You, J. *Organometallics* **2016**, *35*, 1350-1353.

[147] Manda, S.; Nakanishi, I.; Ohkubo, K.; Uto, Y.; Kawashima, T.; Hori, H.; Fukuhara, K.; Okuda, H.; Ozawa, T.; Ikota, N.; Fukuzumi, S.; Anzai, K. *Chem. Commun.* **2008**, 626-628.
[148] Lade, D. M.; Pawar, A. B.; Mainkar, P. S.; Chandrasekhar, S. *J. Org. Chem.* **2017**, *82*, 4998-5004.
[149] Inamoto, K.; Kadokawa, J.; Kondo, Y. *Org. Lett.* **2013**, *15*, 3962-3965.
[150] Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 3354-3357.
[151] Sun, S.-Z.; Shang, M.; Wang, H.-L.; Lin, H.-X.; Dai, H.-X.; Yu, J.-Q. *J. Org. Chem.* **2015**, *80*, 8843-8848.

Acknowledgements

First and foremost, I would like to extend my sincere gratitude to Prof. Dr. Lutz Ackermann, who has offered me this great opportunity to carry out PhD study here at Georg-August-Universität Göttingen. Thank you for the professional advices and constant encouragements during the past 4 years. In his research group, I have the chance to meet so many fascinating colleagues and friends from different cultures, which would be a valuable treasure for my whole life.

I am very grateful to Prof. Dr. Franc Meyer for kindly accepting to be the second supervisor for my PhD study, and also the second reviewer of this thesis. Great gratitude for Prof. Dr. Manuel Alcarazo, Prof. Dr. Inke Siewert, Dr. Franziska Thomas, Prof. Dr. Ulf Diederichsen, who have agreed to attend my defense.

I gratefully acknowledge China Scholarship Council (CSC) for the 4 years financial support during my research stay in Germany.

I deeply thank Torben Rogge, Joachim Loup, Alexander Bechtoldt, Nicolas Sauermann, Thomas Müller, Dr. Svenja Warratz, Dr. Mélanie Lorion, Julian Koeller, Nikolaos Kaplaneris, Tjark Meyer, Matteo Virelli, Shou-Kun Zhang, Zhigao Shen, Wei Wang and Cong Tian, for their patience and time to correct this thesis.

I deeply thank Ms. Gabriele Keil-Knepel for her patience with all the paper work and kind help whenever I encountered any problem in daily life. I thank Mr. Stefan Beußhausen for the technical assistance with the computer, software and network and Mr. Karsten Rauch for his helpful suggestions concerning the lab work. I would like to thank all the members of the analytical departments at the Institute of Organic and Biomolecular Chemistry.

I'm also deeply indebted to all my enthusiastic lab mates—Dr. Wenbo Ma, Dr. Karolina Graczyk, Dr. GarmarcoTenti, Dr. Jie Li (Jack), Dr. Sebastian Lackner, Alexander Bechtoldt—in 308/116 and for their help and encouragement in the past four years.

I am grateful to all the other people in the last four years during my chemistry studies, for their direct and indirect help to me. They are: Dr. Emelyne Diers, Dr. Megha Joshi Yadav, Dr. Christoph Kornhaaß, Dr. Karolina Graczyk, Dr. Carina Tirler, Dr. Suman De Sarkar, Dr. Vladislav Kotek, Dr. David James Burns, Dr. Milica Feldt, Dr. Jonathan Hubrich, Dr. Keshav Raghuvanshi, Dr. Alan James Reay, Dr. Gianpiero Cera, Dr. Debasish Ghorai, Dr. Fabio Pesciaioli, Dr. Santhi Vardhana Yetra, Dr. Joao Carlos Agostinho de Oliveira, Dr. Phani Kumar Nekkanti, Dr. Parthasarathi Subramanian, Darko Santrač, Sachiyo Nakanowatari, Tobias Haven, Marc Moselage, Michaela Bauer, Dr. Daniel Zell, Alexandra Schischko, Korkit Korvorapun, Uttam Dhawa, Valentin Müller, Ralf Alexander Steinbock, Isaac Choi…

During my stay in Germany, I also enjoyed the friendship with my Chinese colleagues and friends–Dr. Weifeng Song, Dr. Lianhui Wang, Dr. Yingjun Zhu, Dr. Qing Gu, Dr. Jie Li, Dr. Fanzhi Yang, Dr. Weiping Liu, Zhixiong Ruan, Hui Wang, Qingqing Bu, Dr. Hongjun Ren, Dr. Xu Tian, Cuiju Zhu, Dr. Yufeng Liang, Dr. Huawen Huang, Jiayu Mo. Thank you all for your support in daily life as well as in chemistry research.

Last but not least, Special thanks should go to my beloved family, especially my wife Shuifeng Yuan and my son Xiaoyu Mei, thank you for your accompany in Germany during the last three years.

Ruhua Mei (梅汝槐)

Curriculum Vitae

1. Personal information

Name: Ruhuai MEI

Date of Birth: August 6th, 1987

Place of Birth: Huanggang, Hubei (P. R. CHINA.)

Gender: Male

Nationality: Chinese

2. Education

09.2013–Present **PhD Candidate in Organic Chemistry**
Institut für Organische und Biomolekulare Chemie,
Georg-August-Universität Göttingen
Supervisor: Prof. Dr. Lutz Ackermann
Thesis: Ruthenium- and Cobalt-Catalyzed Chelation-Assisted C–H Functionalization

09.2010–07.2013 **M. Sc. in Natural Medicinal Chemistry**
West China School of Pharmacy,
Sichuan University
Supervisor: Prof. Dr. Liang Xu
Thesis: Synthesis of the10-Azatricyclo[3.3.2.$0^{4,8}$]decane Core of C_{20}-Diterpenoid Alkaloid Racemulsonine *via* Iodine(III) Promoted Transannular Aziridination Reaction

09.2006–07.2010 **B.Sc. in Chinese Materia Medica**
College of Pharmacy,
Chengdu University of Traditional Chinese Medicine

3. Publication

(1) **R. Mei**, S.-K. Zhang, L. Ackermann*, Ruthenium(II)-Catalyzed C−H Alkynylation of Weakly-Coordinating Benzoic Acids. *Org. Lett.* **2017**, *19*, 3171–3174.

(2) **R. Mei**,' S.-K. Zhang,' L. Ackermann*, Concise Synthesis of Lamellarin Alkaloids by C–H/N–H Activation: Evaluation of Metal Catalysts in Oxidative Alkyne Annulation. *Synlett.* **2017**, *28*, 1715–1718. ('Co-first author)

(3) S. Nakanowatari, **R. Mei**, M. Feldt, L. Ackermann*, Cobalt(III)-Catalyzed Hydroarylation of Allenes *via* C−H Activation. *ACS Catal*. **2017**, *7*, 2511-2515.

(4) **R. Mei**,' C. Zhu,' L. Ackermann*, Ruthenium(II)-catalyzed C–H functionalizations on benzoic acids with aryl, alkenyl and alkynyl halides by weak-O-coordination. *Chem. Commun.* **2016**, 52, 13171-13174. ('Co-first author)

(5) W. Liu,' S. C. Richter,' **R. Mei**,' M. Feldt, L. Ackermann*, Synergistic Heterobimetallic Manifold for Expedient Manganese(I)-Catalyzed C–H Cyanation. *Chem. Eur. J.* **2016**, *22*, 17958–17961.

(6) **R. Mei**, L. Ackermann*, Cobalt-Catalyzed C–H Functionalizations by Imidate Assistance with Aryl and Alkyl Chlorides. *Adv. Synth. Catal.* **2016**, *358*, 2443-2448. (Selected as VIP paper)

(7) **R. Mei**, H. Wang, S. Warratz, S. A. Macgregor*, L. Ackermann*, Cobalt-Catalyzed Oxidase C–H/N–H Alkyne Annulation: Mechanistic Insights and Access to anti-Cancer Agents. *Chem. Eur. J.* **2016**, *22*, 6759-6763.

(8) **R. Mei**,' J. Loup,' L. Ackermann*, Oxazolinyl-Assisted C−H Amidation by Cobalt(III) Catalysis. *ACS Catal.* **2016**, *6*, 793-797. (Co-first author)

(9) W. Ma, **R. Mei**, G. Tenti, L. Ackermann*, Ruthenium(II)-Catalyzed Oxidative C–H Alkenylations of Sulfonic Acids, Sulfonyl Chlorides and Sulfonamides. *Chem. Eur. J.* **2014**, *20*, 15248-15251.

(10) **R. Mei**,' Z. Liu,' H. Cheng, L. Xu*, F. Wang. *Synthesis of the 10-Azatricyclo[3.3.2.0^{4,8}]decane Core of C_{20}-Diterpenoid Alkaloid Racemulsonine via Iodine(III) Promoted Transannular Aziridination Reaction*. *Org. Lett.* **2013**, *15*, 2206-2209. ('Co-first author)